Publication Number 308
AMERICAN LECTURE SERIES®

A Monograph in
The BANNERSTONE DIVISION *of*
AMERICAN LECTURES IN DERMATOLOGY

Edited by
ARTHUR C. CURTIS, M.D.
Chairman, Department of Dermatology and Syphilology
University of Michigan Medical School
Ann Arbor, Michigan

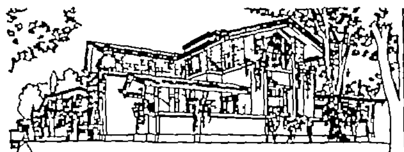
KAPOSI'S SARCOMA

Multiple Idiopathic Hemorrhagic Sarcoma

By

SAMUEL M. BLUEFARB, B.S., M.D., F.A.C.P

Associate Professor of Dermatology Northwestern University Medical School
Attending Dermatologist and Chairman, Department of Dermatology
Cook County Hospital
Attending Dermatologist, Veterans Administration Research Hospital
Assistant Attending Staff Chicago Wesley Memorial Hospital
Chicago, Illinois



CHARLES C THOMAS PUBLISHER
Springfield Illinois U.S.A.

CHARLES C THOMAS PUBLISHER
Bannerstone House
301 327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD., OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

Library of Congress Catalog Card Number 57 5594

Printed in the United States of America

TO RICHARD

INTRODUCTION

In the eighty-six years since Kaposi first described Multiple Idiopathic Hemorrhagic Sarcoma, the disease has continuously stimulated interest. In the course of time every conceivable facet of the interesting disease has been recorded and discussed racial incidence, age and sex predisposition, terminology and nosology possible causative factors, pathogenesis, symptomatology hematologic aspects and treatments. There is, as a result, a voluminous literature on the subject, so large that to keep abreast of it is almost impossible. Dr Bluefarb, in undertaking to review and to assess critically this vast fund of accumulated knowledge, has rendered an invaluable service.

Gathering the material for this monograph was obviously a laborious task. It is not important that he is unable to ascribe the disease to a single cause- it is not important that his discussion of treatment ends on a depressing note. It is important that all available facts are here recorded in one small monograph. In this easily accessible book is a critical analysis of the various views as to the cause of the disease, a sober appraisal of the various therapies that have been suggested, indeed, a full consideration of every phase of the disease—and also, many little-known facts are herein recorded.

Dr Bluefarb is uniquely fitted for the task for he has long been a serious student of the cutaneous manifestations of lymphomas and of so-called reticuloendothelial diseases. He has contributed significantly to the literature of this subject. He has presented the material in this monograph on Kaposi's sarcoma simply and in logical sequence It should long serve as an authoritative source of reference

Herbert Rattner M D



1 Moritz Kaposi (1837 1902) A previously unpublished photograph (through the courtesy of Paul E Bechet, M D and Arthur C. Curtis, M.D)

I

HISTORICAL

In 1872 Kaposi (132a) first described a condition which he named "Idiopathic Multiple Pigment Sarcoma of the Skin." The present designation of "Kaposi's Sarcoma" was suggested by Koebner (137b) in 1891. Kaposi agreed to this designation, but twenty years later (132b) changed it to "sarcoma idiopathicum multiplex hemorrhagicum," a name he believed was more accurately descriptive of the condition, and would also indicate the source of pigment (hemosiderin) in the lesions. In his classical description of the disease, Kaposi noted the symmetry and multiplicity of the lesions from the onset as a characteristic of the disease. This report was based on five cases, but he later added 20 cases which he had observed. He regarded the disease as distinctive and believed it to be a special and peculiar form of round cell sarcoma, which occasionally presented characteristic spindle cells.

II

SYNONYMS

THE VARIETY of descriptive terms suggested since Kaposi's original report give evidence of the varied conceptions of this disease. There are differences regarding the histologic changes of the various lesions in one individual, as well as in portions of the same lesion, which accounts, in part, for the various theories about this disease.

Year	*Writer*	*Synonyms*
1868	Kaposi	Primaren idiopathischen hautsarcoma
1872	Kaposi	Sarcoma idiopathicum multiplex pigmentosum
1878	Tanturri	Sarcoma idiopathicum telangiectodes
1883	Hardaway	Sarcoma cutis
1884	Babes	Angiosarcoma perithelilale fusocellulare
1889	Funk	Sarcomatosis gummatoides
1891	Köebner	Sarcoma idiopathicum multiplex hemorrhagicum der extremitaden
1894	Kaposi	Sarcoma idiopathicum multiplex hemorrhagicum
1894	Unna	Acrosarcoma multiplex cutaneum telangiectodes
1898	Tommasoli	Primitives hemorrhagisches acrosarcoid
1899	Bernhardt	Sarcomata idiopathica multiplicia pigmentosa cutis

Year	*Writer*	*Synonyms*
1899	Gilchrist	Angiosarcoma
1899	Pospelow	Acroangioma hemorrhagicum
1899	Sellei	Granuloma multiplex hemorrhagicum
1901	Radaeli	Angioendothelioma cutaneum
1902	Lieberthal	Multiple idiopathic hemorrhagic sarcoma
1903	Pelagatti	Acrosarcoma
1910	Sequeira	Granuloma angiomatodes
1912	Rasch	Sarcoma cutaneum telangiectaticum multiplex
1912	Sternberg	Kaposi's sarcoma
1913	Martinotti	Sarcoma hemangioendotheliale intravasculare
1915	Sibley	Granuloma multiplex hemorrhagicum
1917	Gaucher	Sarcomatosis primitiva telangectosica
1922	Bertaccini	Angioendothelioma cutaneum
1925	Guiffre	Sarcomatosis telangiectatica cutanea idiopathica generalisata
1926	Guarini	Multiple angiosarcoma
1927	Hamdi and Halil	Perithelioma multiplex nodulosum cavernosum lymphangiectodes cutaneum
1928	Hudelo, Caillian & Chene	Pseudosarcomatosis telangiectatica
1928	Pautrier and Diss	Pseudosarcoma (kaposi) myoneurovascular dysgenesis
1928	Nicholas and Favre	Sarcomatose telangioctatique pigmentaire
1931	Tramontano & Fittipaldi	Hemangioendothelioma cutaneum
1932	Hamdi & Resat	Acroperithelioma idiopathicum multiplex cavernosum lymphangiectodes cutaneum

Year	*Writer*	*Synonyms*
1934	Kusnezow	Endoperitheliome sarcomatodes multiplex idiopathicum (typus Kaposi)
1935	Lang & Haslhofer	Systematized angiomatosis
1939	Choisser & Ramsey	Angioreticuloendothelioma
1953	Ronchese and Kern	Angioreticulomatosis

III

ETIOLOGY

A. Incidence and Sex

KAPOSI'S SARCOMA appears to be relatively common in cosmopolitan areas such as New York City and Chicago as well as in such countries as Italy Poland and Russia. In a review of the literature, Dorffel (56) found reports of 358 proved cases and added 16 cases. The total is undoubtedly higher than these figures indicate since, in many large cities, Kaposi's sarcoma is not reported unless the patient exhibits unusual manifestations of the disease. Of the 356 cases reported in the literature, Dorffel found 325 were men (five under 20 years of age) and 21 were women, all adults. He tabulated all cases reported up to 1951 in which the age was given, a total of 360 cases, which probably offers a fair representation of the age incidence of Kaposi's sarcoma.

Decade	*Cases*	*Per Cent*	*Decade*	*Cases*	*Per Cent*
First	5	1.4	Sixth	83	23.0
Second	10	2.8	Seventh	94	26.1
Third	21	5.8	Eighth	45	12.5
Fourth	32	8.9	Ninth	11	3.1
Fifth	59	16.4			

The incidence is highest between the ages of 50 and 70 years, being less frequent in young adults and rare in children. It is known that this disease usually affects older persons and is much more common in men than in women. However younger persons are not immune The first symptoms may

appear early in life while the typical full syndrome occurs at a later date.

Of the 434 patients reported up to 1939 Choisser and Ramsey (40) found only 5.9 per cent were women. From that date to 1950 we found 144 additional cases in which the sex was given, among which there were 15 women, or 9 6 per cent of the total. Therefore, it seems apparent that between 6 and 10 per cent of all cases reported occur in women.

An instance of the disease affecting several members of a family was reported by Greco (95) His patient was a 63 year old man whose two brothers had died of the disease and a son of one of these brothers had just developed the condition. The patient had the classical picture of Kaposi's sarcoma for five years.

B. Occurrence in the Young

Kaposi's sarcoma rarely affects children, only eight cases occurring in the first decade of life have been recorded Kocsard (136) described an eight year old Chinese boy and Dorffel (56) reported a boy who developed the disease following trauma at the age of six years. McLean's (157) patient was a five and one-half year old child who presented a symmetrical, deep purplish discoloration of the face: the cheeks were markedly edematous, hard and tense and this condition extended up to the lower lids and down to the lower lip and chin. The lips were indurated and pigmented, and there was a slight hemorrhage in the subconjunctiva of the left eye.

The youngest patient was recorded by Chargin (39b) who stated that he had observed a six month old infant with Kaposi's disease A patient having the onset at five years of age was presented at the Dermatological Conference of the Mississippi Valley and Central States Dermatological Association (37) This patient also had osseous changes in the left pubic bone, left ilium and the humerus. Graham-Little (94) described a woman who had developed the disease at the age of eight years. Denzer and Leopold (54) reported a four

and one-half year old American boy of Italian parentage, who developed two blue spots on his left leg which were attributed to trauma. There were two purplish raised painless nodules, each 2 cms. in diameter on the middle third of the left leg and several dark, firm purplish plaques on the ankles. Histologic examination revealed Kaposi's sarcoma. The lesions did not respond to roentgen ray therapy and the patient died five months later The diagnosis was confirmed at autopsy

Kessel (133) described a 6 year old Bantu boy who had no cutaneous lesions and the diagnosis was made on histologic examination of a lymph node and the spleen.

The occurrence of Kaposi's sarcoma in the second decade was reported by Senear and Wien (232b) in a 15 year old girl. Corson and Knowles (47) described two cases, one a 17 year old boy and the other a 15 year old girl Senear and Caro (232a) reported a 16 year old Italian girl and Silvers (239a) patient developed the disease at 14 years of age. The patient reported by Bechet (14) was 18 years old and the case presented by Hedge (114) was an 18 year old boy

C. Geographical Distribution

The widespread *impression that Kaposi's sarcoma is limited* almost exclusively to Jews is now believed to be erroneous. On the basis of studies reported in the literature and personal observation, we do not believe that the race of the patient is an etiological factor in this disease We are in agreement with Dorffel (56) *who states that the distribution of the disease* is geographical rather than racial, since the vast majority of patients appear to be Russian, Polish or Northern Italian.

Wise (255a) found that the cases recorded in New York City were almost all men of Italian or Galician birth. Among 50 patients from Northern Italy reported by De Amicis (53) none were Jewish. In the literature Dorffel (56) found 111 Italian, 50 Russian, 20 Polish, and 45 Jewish patients, most of whom were born in Russia or Poland but they were not included with either the Russian or Polish groups *in the sum-*

mary There were also 12 Austrians, 8 Americans, 7 Hungarians and 5 Germans, while the remainder of the 356 patients represented nearly every nationality in the civilized world. Among 62 patients described by Choisser and Ramsey (40) they found 12 were Italian and 12 Jewish while 16 were from diverse localities and in 22 cases the locality was not mentioned. The disease appears to occur less frequently in Germans, Scandinavians, English and Americans. However McCarthy and Pack (153) found 30 (83 per cent) of the patients in their series were Jews or Italians, regardless of nativity whereas arranged on a geographical basis, Eastern Europe was represented by only 74 per cent, practically all of whom were Jewish or Italian. Although the high incidence of Jews and Italians in New York City should be considered, they believe that these findings support the theory of racial or biological proclivity

In their series of 36 cases, McCarthy and Pack (153) found eight patients (22 per cent) to be American born. Lane s (144) patient was a native American man whose family had resided here for two generations. In commenting on this case, Kingsbury (134b) stated that he had never before observed this disease in a native American.

The patient described by Gillet (88) was a 30 year old Mohammedan man and Gougerot, *et al* (92b) reported a 30 year old Armenian women. Kocsard's (136) patient was a Chinese student who developed the disease at eight years of age and Epstein s (65) case was the first to be reported in a Japanese woman. The first report from India, occurring in a Hindu, was that of Banerjee (12)

Kaposi's sarcoma appears to be comparatively rare in the Negro race Ellis (64) patient was a full-blooded Negro who was a native of the United States. He presented numerous pigmented, non-scaly macules, up to 1 cm in diameter on the chest and abdomen, and many firm, painless cutaneous and subcutaneous nodules of 3 mms. to 2 cms. in size, on the arms and legs. Lowenthal (152) described a full blooded Negro

who had about a dozen nodules on the foot and around the ankles. Garner's (86) patient, a 54 year old Negro had discrete and confluent, deeply pigmented nodules and plaques on all the extremities, elephantiasic changes of the feet and deep purplish lividity of the hands. A 56 year old American Negro, reported by Symmers (254a) had a painful indurated area on the finger not the result of injury There were several bluish red nodules on the left hypothenar eminence and similar cutaneous nodules at the tip of the little finger on the right hand as well as large nodulated plaques on the thenar eminence and in the palm There was a series of nodules along the hypothenar eminence and a small plaque on the right wrist joint, just above the palm, and twenty or more similar nodules, each about 0.5 cms. in diameter on both ankle joints. Aegerter and Peale (2) reported a 60 year old Negro who had attacks of paroxysmal dyspnea which often awakened him from sleep. His heart was moderately enlarged to the left, and there was a blowing systolic murmur at the apex, transmitted to the axilla. The liver was enlarged. He died suddenly and autopsy disclosed the pericardial sac to be immensely dilated with over a liter of fresh, unclotted blood. The heart showed moderate concentric hypertrophy Arising from the wall of the right atrium just distal to, and to the base of the right auricle, was a nodular hemorrhagic tumor mass, measuring 4 cms. at the base. Just distal to, and to the right of this region, a somewhat smaller tumor arose from the right arterial wall down to the anterior surface of both the right and left side of the heart, and up over the conus arteriosus and, at the base of the aorta, there were numerous plaques of tumor tissue. However Symmers (254b) stated that he had examined the histological sections of the cardiac tumors and disagreed with the diagnosis of Kaposi's sarcoma.

A 61 year old Negro who had developed small tumors on both feet nine years previously was described by Brunsting (30) The lesions progressed to involve the entire sole and toe of the right foot and the instep of the left foot. There

were numerous pea sized and larger round, firm cutaneous nodules, pink to brownish in color distributed over the soles and toes of both feet. A diagnosis of blastomycosis, proved histologically had been made seven years previously Therefore Brunsting believed the most plausible explanation would be that Kaposi's sarcoma developed on the background of an older infectious process. A 43 year old Negro with lesions in the oropharynx was described by Syrop and Krantz (255) Bluefarb and Webster (26c) reported a Negro who had Kaposi's sarcoma of the skin and lymphosarcoma of the lymph nodes. A full-blooded Negro was reported by Persky and Lisa



2 Kaposi's sarcoma occurring in a patient with lymphosarcoma.
3 Kaposi's sarcoma in a Negro.

(196) and Hazen (113) stated that he had observed two Negroes having Kaposi's sarcoma. The occurrence of Kaposi's sarcoma in Negroes has also been described by Pardo-Castello (190) and by Sneid (244) Smith and Samitz (243) described an 85 year old Negro and Andrews (6a) presented an American mulatto with Kaposi's sarcoma.

Findlay (72) believes that Kaposi's sarcoma is not particularly rare in West Africa, since there is an occurrence of at

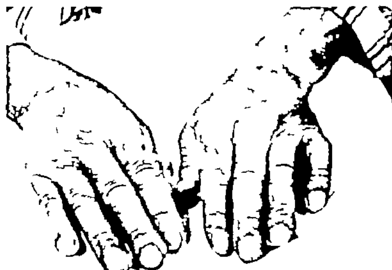
least one case in 50,000 among the young adult population. In 1922, Jojot and Laigret (128) described a Bantu Negro who developed multiple tumors of Kaposi's sarcoma. A native of the Belgian Congo who had nodular lesions on the upper extremities and scrotum was described by Rogowsky (209) who also mentioned that this was the sixth case observed in this geographical area. Kessel (133) described a six year old Bantu boy. Two patients, both Bantu men, were described by Kaminer and Murray (131). They found that 41 cases of Kaposi's sarcoma affecting Bantu men had previously been reported. This relatively high incidence is in striking contrast to the relatively few cases reported in American Negroes and, therefore, they considered the possibility of a genetic factor.

D. Predisposing Factors

There appears to be a definite relationship to certain predisposing factors such as general or local vascular lesions, sclerosis, ectasiae, hemorrhagic diathesis, edema, trauma and alcoholism. A prodromal stage is marked by local cyanosis, edema and slight inflammation, or by definite vascular ectasiae.

According to Pack (188b), these patients exhibit a common physical habitus, namely, flat feet, short sturdy legs, thick ankles, tight inelastic skin and coexistent or antecedent circulatory disturbances of the lower extremities, such as varicosities and edema. The legs usually show varicosities and nodular bleeding of the peripheral vessels, another indication of the vascular origin of this tumor.

Recent studies indicate lymphedema as a factor in the genesis of angioblastic sarcoma, according to McCarthy and Pack (153), who state that lymphangiosarcomas of the upper extremity developing in surgical elephantiasis, are identical with Kaposi's sarcoma. Stewart and Treves (249) reported lymphangiosarcoma developing in the edematous arms of six women whose elephantiasis, following mastectomy, had been present from six to 24 years. They speculated on a common systemic carcinogenic factor responsible not only for the angio-





4. Kaposi's sarcoma in a Negro.
5. Typical localization of Kaposi's sarcoma.

sarcoma of the arm, but also for the primary carcinoma which led to radical mastectomy. All six patients had cutaneous lesions which resembled Kaposi's sarcoma both clinically and histologically. Two similar cases were reported by Aegerter and Peale (2) and by Hansson (108). Both women developed Kaposi's sarcoma of the lower extremities nine and 29 years, respectively, after the onset of massive lymphedema which had resulted from infection. The prolonged lymphedema, in both cases, appeared to constitute the sole known predisposing factor since no other primary neoplasm had previously been detected.

1. Occupation. Approximately 95 per cent of the reported cases are of the "laboring" class and a scant 5 per cent are "white collar" workers, according to Van Cleve and Hellwig (265). Sequeira (233a) commented on the fact that most patients are men of powerful build. The "laboring" class patients include those exposed to extremes of temperature as well as those who do manual labor. It has never been adequately explained why office workers and professional persons are less frequently affected than laborers, unless the element of trauma is more prone to occur in the latter group.

It is the opinion of McCarthy and Pack (153) that the laboring occupation does not necessarily predispose to Kaposi's sarcoma, but rather that the occupation requires the patient to be on his feet for long periods of time. This is further emphasized when it is noted that most patients develop the initial tumor on the feet or legs, and often have an associated edema.

2. Trauma. Mechanical, toxic or infectious injury may also be a factor. Examples of mechanical injury preceding the development of Kaposi's sarcoma in the injured area are frequently recorded. Lieberthal (151a) described a man who had injured his leg and, one month later, painful swelling and nodules developed on the injured leg, which was the first symptom of the disease. Ledermann's (147) patient developed typical nodules on the arm following a horse bite

three years previously New nodules appeared in this area after a short time. Ormsby and Mitchell (186a) reported a 56 year old Swedish man who developed the disease following gnat bites. Weber and Daser (273b) described a patient who developed nodules of the disease after stepping on a nail. Hedges (114) patient, an 18 year old boy had pierced the right foot with a nail nine years previously The man reported by Sibley (237) had cut his hand slightly on a tooth when dealing a blow eight years before. A small red spot appeared immediately afterward, which had gradually increased in size and, 18 months later a pigmented lesion appeared on the back of the hand. Later the feet and ankles became involved and the condition gradually spread upward to the face, while the head and neck were the last areas to be involved by tumors. Pick (198a) Wallhauser (268) Zumbusch (291) Dalla Favera (52) Chargin (39a) Jeanselme (126) and Feit (70) have also recorded cases in which there was little question of the relationship between mechanical injury and the subsequent appearance of tumors in the injured areas and, subsequently in the typical distribution of the disease.

3. *Cold.* Exposure to cold has been mentioned as a factor in the development of nodules of Kaposi's sarcoma. Semenow (231) observed 10 cases, within a five year period, and noted that a large proportion of these patients had been exposed to more or less severe and prolonged cold and he was inclined to attribute a causative influence to this factor In one of his cases the bluish nodules occasionally disappeared spontaneously but always reappeared in cold and damp weather Vague types of erysipelas, immediately preceding the appearance of nodules of Kaposi's sarcoma, as well as lymphangitis and cellulitis, have been reported.

4. *Vascular Changes.* Arteriosclerosis and other vascular changes, such as those present in syphilis, have been reported frequently The vascular changes are usually found at autopsy but their high incidence is probably explicable on the basis of the advanced age of the patients, according to Dorffel (56)

In some cases, no definite preceding factor was found, but often vague, prodromal symptoms were present, such as rheumatic pains, which are recurrent and subject to variations in weather as mentioned by Steiner (247) and others. Pelagatti (194 case 1) described a patient having paralysis of one side of the body and it was on this paralyzed side that Kaposi's sarcoma first developed. The condition always remained more severe on this side while less severe manifestations were present on other areas of the body The patient described by Uhlmann (262) had fractured the upper arm with resulting paralysis. This extremity was first affected by Kaposi's sarcoma.

5. *Arsenic.* A patient who developed Kaposi's sarcoma apparently following an erythema from arsphenamine, was described by Leigheb (148) A 76 year old man who had Kaposi's sarcoma for 17 years was reported by Eljasz (62) He developed a cutaneous horn following intravenous injections of an arsenical (Solarson) This horn was removed and histological examination revealed typical Kaposi's sarcoma.

E. Sites of Predilection

The skin is the most frequent site of predilection in Kaposi's sarcoma. The cutaneous surface of the lower and upper extremities are most frequently involved (75 to 85 per cent of the cases) although no area of the cutaneous surface is exempt. The next most frequent sites of involvement are the submucosa of the entire gastrointestinal tract, the external genitalia, the superficial and deep lymph nodes (especially the retroperitoneal and mesenteric) liver and lungs. Less common sites of involvement are the tonsils, bones, larynx and conjunctivae. Uncommon sites include the spleen, pancreas, kidneys, adrenals, testes, epididymis, trachea, bronchi and pleura. Lesions are extremely rare in the heart, central nervous system, peripheral nerves, tongue, bladder muscles, pituitary gland and brain, while involvement of the thyroid gland, ovary or uterus has never been reported.

1 Extremities. Kaposi's sarcoma has a marked tendency to localize on the extremities, and develops symmetrically with a typical arrangement. The cutaneous lesions at first appear on the hands and feet, then on the forearms and legs, and later include the arms and thighs. Primary cutaneous sarcomata, localized in this manner may be regarded as the Kaposi type. (Frohlich: 83)

In eleven of Hansson's (108) patients, the first nodule appeared on the feet, in six the first manifestation was on the hands, and two had primary lesions on the lower legs. Pick (198a) also described the first localization on the lower legs. Stats (246) reported a case in which the disease was limited to the hands. Philippson (197) and Dalla Favera (52) con-



6 Bilateral lesions of Kaposi's sarcoma showing tendency toward symmetry

sider the extremities as well as the external genitalia, common sites of the disease

The eruption is usually unilateral at first, then becomes bilateral with a tendency toward symmetry as the disease progresses. Symmetrical involvement of both lower extremities is designated stocking distribution. Occasionally the condition is generalized The lesions are most numerous at the

peripheral ends of an extremity and become sparser near the trunk, which is rarely involved until late in the disease when the internal organs are also involved.

Symmers (254a) states that while the distribution of the cutaneous lesions are of interest, their significance is not clear He found that lesions occur in greatest abundance in the skin immediately covering the bone and in lesser numbers in the skin over soft tissues. Most often the lesions first appear on *the lower extremities, not uncommonly they may first appear* on the fingers, around the wrists and on the affected extremities. The plateau-like formations usually attain their greatest size in the immediate vicinity of the joints; notably the small joints of the hands and feet. The cutaneous lesions appear to have a predilection for the less flexible skin areas having a less plentiful blood supply and appear to avoid the more easily movable skin areas which have a more abundant supply of blood.

A 78 year old man, presented by Morso (174) first developed lesions on the toes and feet eight years previous to the development of lesions on the dorsum of the hands. Gougerot and Burnier (92a) described a 40 year old man who had nodular lesions, localized only on the palms, of three months duration. Gonzales and Vidaurreta (91) reported a 55 year old Italian who first developed a small tumor on the index finger Three months later numerous other nodules appeared on the dorsum of the hands, forearms, feet and lower legs. Some lesions were slightly ulcerated, and others tended to form confluent tumors. There was a generalized edema of the hands and feet and nodules in the lobe and pinna of the right ear Costello (48b) presented a patient with a soft, compressible telangiectatic, marble-sized lesion on the right palm which was thought to be a granuloma pyogenicum. Zakon (259a) described a 63 year old man who had developed dusky and sharply outlined, infiltrated plaques on the dorsum of the right hand seven years previously

Forman's (79a) patient was a 56 year old man whose only lesions were an eruption on the small finger of the left hand

which slowly extended to form a patch of purplish infiltration, fairly sharply defined, on the back of the hand, and similar areas on the fingers. A 21 year old man, reported by Forman (79b) had the initial lesions on the ulnar border of the right hand while, at the same time, lesions occurred on the left heel. Roxburgh and Klaber (215) presented a 41 year old man who developed coalescent groups of raised, firm, smooth, dis-



7 Nodule on the toe as the first manifestation of Kaposi's sarcoma.
8 Nodular angiomatous lesion of the arm resembling granuloma pyogenicum.

crete, purple nodules, covered by a thin loose scale on the right middle toe and immediately proximal to this toe. The nail was grooved and largely occluded by two superimposed angiokeratoma, arising from the superficial aspect of the nail fold.

All of the cases originally described by Kaposi, and most of those observed since, have exhibited some degree of symmetry Klaber (135c) described a 32 year old woman in whom the disease had remained unilateral two years after onset.

The 63 year old Polish man, described by Kingsbury (134a)

developed the eruption on the left index finger one and one-half years previously and on the right foot nine months later The skin of the affected areas was purplish in color with numerous hemorrhagic nodules. Rattner and Neuhauser (204) presented a 59 year old man who first developed a lesion on the right thenar eminence four and one-half years before the appearance of a small lesion on the right lower extremity which gradually increased in size and new lesions appeared from time to time on the extremities and left buttock.

Finnerud's (73a) patient, a 29 year old Hungarian woman, developed the initial lesion, a hard red nodule, on the latero-posterior surface of the right arm. There were two lesions each on the right and left thigh and left leg, and one each on the right leg, shoulder and scalp. Frost (83) described a 48 year old man whose lesions appeared first on the hands, later on the legs, and subsequently on the toes, ears and body The lesions were accompanied by edema of the hands and feet. There was also one lesion on the right eyebrow and one on each ear Webster (274) described a 77 year old man who had involvement of the right hand and, to a slight degree, of the right forearm for six years preceding his death. Along with a relatively few other similar cases, this indicates that, aside from the type originally described by Kaposi, the condition may be encountered with a single or a few localized efflorescences, frequently only on one side of the body which remain for an extended period before extension occurs.

A patient having a small, rose red spot on the left hand, which largely disappeared on pressure, was reported by Selhorst and Polano (229) The disease had apparently remained stationary for about 18 years, after which there was a relatively rapid extension, so that, 20 years after onset, lesions on both the hands and feet were clinically and histologically typical of Kaposi's sarcoma. Kreibich (138) described a patient having only two cutaneous lesions both on the right foot. Braun and Scuffer (28) reported a case from the clinical records and moulages of Frieboes, in which the lesions were almost entirely restricted to the right hand, there being only slight

involvement of the left, and one lesion on another part of the body. In Mierzecki's (169 case 1) patient, the disease was still confined to the right hand and elbow two years after onset. Cattaneo (38) observed two patients, both having a single lesion, in one case on the right leg, and in the other on the left leg. In the case described by Senear and Wien (232b) the manifestations of the disease were restricted to the left foot and ankle.

2. Scalp, Face and Ears. A 72 year old man who had multiple small tumors on the face was described by Stillians and Smith (250). A large, hard, purple tumor mass had been



9 Lesions on the face resembling leukemic nodules.
10 Lesions on the face resembling leukemic nodules.

excised from the right side of the nose six years before. Three years later a small purple mass had appeared on the right wrist and dorsum of the left hand. Symmers' (254a) patient, a 68 year old man, had vague gastrointestinal symptoms for seven years and a small pruritic growth on the auricle of the right ear. A similar growth had been removed from the same area a year previously. There were recurrent, unilateral lesions

in the auricle of the right ear without corresponding changes in other parts of the body

A 65 year old man, described by Jessup (127) had only two lesions; one on the scalp, the other on the forehead. These small painless lesions had appeared four months before, and the scalp lesion was diagnosed as a cyst. It was removed surgically but failed to heal and new lesions continued to appear The unusual location in the scalp, without nodules or plaques elsewhere on the body *made the clinical diagnosis*



11 Nodule on the ear resembling granuloma pyogenicum.

difficult. Wise (255a) described a patient, having a nodule on the nose who also had another nodule on the cheek and lesions on the thighs, feet and forearms. MacKee and Cipollaro (155b) described a patient with a nodule on the ear and discrete nodules on the feet. Rulison (216) reported a 58 year old man who had a small purplish tumor on the outer border

of the right upper eyelid which had been present for eight months. Soon, two similar lesions developed in close apposition to the first, and similar lesions developed on the right ear and neck. Fraser (81c) commented that the histological diagnosis in this case was Kaposi's sarcoma in spite of the unusual location of the lesions. He mentioned that Ewing (66a) observed a patient having a single lesion on the tongue.

Spinner (245) reported a 67 year old man who developed an irritation behind the right ear six months before. Several small nodules appeared a short time later Mitchell's (171) patient, a 44 year old Italian, presented thickened, infiltrated, inflammatory plaques and nodules of 10 years duration on the ears, nose, hands and feet. A patient described by Gilchrist and Ketron (87b case 2) had six distinct lesions on the face five of which, at first glance, appeared to be chronic localized patches of rosacea. The majority of the lesions were present on the lower third of the nose. The two lesions on the right side were semiglobular firm, raised, reddish brown nodules, about 4 mms. in diameter of two years duration. The three lesions on the left side were deep red, smooth, flat, rather linear shaped elevations, deeply infiltrated on palpation, measuring 3 by 6 mms., and had been present for six to eight months. There were lesions on the center of the cheek and chin, present for one month, which were dark red, slightly raised, deeply infiltrated patches, 1 by 1½ cms. in size, and showed no loss of color upon pressure

The usual history according to Crocker (49) begins with diffuse cyanotic spots which pass into infiltrations and then into nodules, with or without preceding odema. Traub (260) reported a 65 year old Italian who first presented a rather large, purplish, ulcerative lesion of the left ala nasi, which was 2 cms. in diameter and elevated 1½ cms. above the surface of the skin. The lesions, present for four months, were peasized, pigmented and vascular and involved the right ear lip and dorsal surfaces of the fingers of the left hand. Dorffel (58 case 8) described a patient in whom the disease first appeared on the eyelids ten years previously with hemorrhages

and nodules. Lesions subsequently appeared on the scalp and face and later became generalized. Another patient (56:case 14) developed lesions on the nose six years previously and later lesions appeared on the fingers and toes.

Epstein (65) reported a patient who first developed purpuric lesions on the right ear A nodule then appeared on this spot which was soon followed by the development of two more nodules close to the original lesion. Becker and Thatcher (15b case 1) described a 52 year old man who was first seen



12. Unilateral lesions on scalp and forehead.

with syphilitic hemiplegia. He presented a few dusky erythematous, semi-globular tumors, up to 0.5 cms. in diameter on the face and chin which had been present for three or four years, and had recurred after complete removal by electrodesiccation.

A 52 year old Swedish man, presented by Bluefarb (26a) first developed a nodule on the left ear seven months before the appearance of nodules on the left side of the scalp and forehead corresponding to the ophthalmic branch of the trigeminal nerve.

In cases reported by Perrin (195a) and by Funk (84) the initial efflorescences were on the cheeks and nose. Hansson (108) described three patients having the initial tumor on the nose. His first patient, a 44 year old man, had a tumor of the left nostril which had gradually increased in size for two months. The lesion bled occasionally but caused no other symptoms. It was reddish, scab-encrusted and about the size of a pea. He was unable to find previous reports of such a primary localization. Kaposi and several other investigators definitely state that nodules appear on the face only at a much later stage of the disease. In a series of 16 cases, Ronchese and Kern (210b) noted that two patients had lesions on the ears, one on the face and one on the scalp.

3. *Oral* The mucous membrane of the mouth is believed to be one of the most common localizations in the more advanced stages of the disease, according to Philippson (197) Bernhardt (19) and Sellei (230) The growths in the visible mucous membrane always appear to be associated with similar cutaneous growths, and were it not for this association, might easily escape clinical identification, according to Symmers (254a) The palate, especially the hard palate, seems to be the most common site of involvement in the mouth, although patients with hemorrhagic lesions in the soft palate and gums were reported by Kingsbury (134a) and Sequeira (233c) Lesions occurring on the hard palate as an elongated, purplish plaque situated transversely across the roof of the mouth and involving the posterior aspect of the hard palate,

were described by Wise (255c) Kusnezow (142) described a patient with nodules on the left side of the hard palate and one on the upper lip which was the size of a cherry At autopsy there were two pea sized bluish nodules present at the base of the tongue. In the case described by Beerman and Tavs (17) the patient had a purplish nodule on the left side of the hard palate. Gross (101) patient had lesions on the hard palate and lower lip in addition to other lesions. Downing (57) also described such a case. The first manifestation of the disease occurred on the hard palate in the case of



13. Discrete nodules on the hard palate.

Kaposi s sarcoma of the bone reported by Feit (70) Two of Hansson s (103) patients had lesions localized on the face one of whom also had bluish-red infiltrations in the hard palate Bluefarb and Rodin (26b) also observed two patients having lesions on the hard palate.

Silvers (239a) presented a man who had an ulcerating egg

sized mass on the right tonsil. Feldman's (71a) patient had a solitary lesion on the hard palate. Stats (246 case 2) described a patient with two 2 mm bluish tumor nodules on the left side of the tongue, just behind the sulcus terminalis.



14. Group of angiomatous nodules involving the hard palate.
15. Close-up view of illustration 14.

Araux, *et al.* (7) reported nodules on both lips, the palate and the dorsum of the tongue. Grzybowski (102) reported involvement of the tongue. Roger and Vigne's (208) patient had involvement of the lips and the patient described by Pearce

and Valker (193) had involvement of the gums. This man developed the disease at the site of an extracted tooth. Cutaneous nodules soon followed. Zakon's (287a) patient had lesions on the soft palate and left tonsil.

Wise (283a) described a patient who had two purplish nodules on the left anterior pillar and on the adjoining hard palate. Stats (248 case 1) reported a pea-sized, circumscribed purplish nodule on the buccal mucosa. The 59 year old Italian man reported by Seagrave (228) had a mass in the nasopharynx.

Conjunctival nodules have been reported in Kaposi's sarcoma and are usually associated with histologically similar growths in other accessible mucous membranes, such as the mouth, pharynx and esophagus, and always, it appears, with corresponding cutaneous changes. A patient reported by Symmers (254a) presented an oval new growth in the conjunctiva immediately adjacent to the upper and outer edge of the left cornea. This lesion was movable and non-pigmented. There was a similar cutaneous growth on the temporal side of the left lower eyelid. The conjunctival lesion in this case is believed the only one thus far recorded in the English literature on Kaposi's sarcoma, and the only recurrent conjunctival growth so far described. Although the cutaneous lesions in Kaposi's sarcoma tend to become symmetric, the conjunctival nodules thus far recorded have been unilateral.

Schmidt (225) presented a 65 year old man with involvement of the oropharynx and larynx. On the soft palate, fauces, and posterior pharynx, there was a sharply marginated, purplish red, raised, edematous lesion. The epiglottis was thickened and involved by the same process; as was also the base of the tongue, pyriform sinus, aryepiglottic fold, false cords and ventricular areas. Sulzberger (253) reported a woman who had a lesion in the left tonsillar area. Ochs (183) presented a 56 year old man who had lesions of the mouth. Dorffel (56-case 7) described a patient who had the typical distribution of the disease as well as involvement of the mucous membranes.

Pautrier and Lassueur (191c) state that lesions in the mouth are very rare and the particular form described by them has not been encountered before. This patient presented vegetative tumor formation with ulceration, the lesions were painless and simulated a carcinoma.

4 Other Areas of Involvement. A 60 year old Italian man, described by Stratton (252) had pain and swelling of the fingers and toes for the previous six months. The skin of these areas was of a purplish red color and board like consistency studded here and there with elevated, hard, purplish red



16 Penile lesions of Kaposi's sarcoma.
17 Penile lesions of Kaposi's sarcoma.
18. Penile lesions of Kaposi's sarcoma. (Courtesy of Francesco Ronchese *Postgrad Med., 14* 101 1953)

nodules. There were similar lesions behind and on the margins of the ears as well as on the penis. The scrotum showed a single, much larger elevated tumor of the same type, 1.5 by 2 cms. in size, which had developed following severe pruritus of this area ten years before. The right inguinal lymph nodes were enlarged. Tumors of the extremities and ears had occurred a few months after exposure to severe cold in Alaska. There was no evidence of tumor formation in the viscera.

Two patients having involvement of the penis were reported by Barringer and Dean (13) The first had two submucus nodules on the penile head, and the second a round, solid-appearing, cherry red growth on the corona. The lesion resembled carcinoma. The patient described by Bluefarb and Webster (26c) had nodules on the penis. Van Cleve and Hellwig (265) reported a 58 year old American man who, four years previously noted a small pimple-like lesion in the left groin. The lesion became larger and painful to pressure and finally receded in six weeks time, leaving a pigmented scar Soon, however a similar lesion appeared in the right groin and numerous smaller lesions appeared over the anterior surface of the extremities. Philippson (197) described a patient who had enormously swollen genitalia and multiple tumors of the penis which interfered with micturition. Stats (246 case 2) patient had a pea sized nodule near the external meatus. Newman (177) described a 75 year old man who had a urethral stricture produced by Kaposi's sarcoma. Agosta (3) reported a 50 year old woman who had involvement of the gluteal region.

IV

PATHOLOGY

A. Pathogenesis

In the present state of our knowledge, it is fruitless to speculate concerning the nature of the etiology of Kaposi's sarcoma. There are nearly as many theories regarding the nature of the origin of this disease as there are investigators in the field. Briefly the opinions may be classified in five major groups 1) neoplasm, 2) infectious granuloma with neoplastic potentialities, 3) systemic vascular disease, 4) derivation from nerve tissue, and 5) reticuloendothial hyperplasia.

The major difficulty in classifying this particular type of lesion is due to the fact that there is no unanimity concerning the origin of the tumor Fibroblasts, perithelial and endothelial cells, myoneural structures of the glomus and reticuloendothelial elements are among those considered by various writers as the starting point of the new growth Most investigators agree that the disease has a multicentric origin, and that lesions in the internal viscera are not metastatic lesions. As evidence they cite the bizarre localizations of the internal lesions, their appearance, in some cases prior to cutaneous manifestations, and, finally the lack of invasive tendencies. Another point, upon which most investigators agree is that it is an affection of vessels, particularly blood channels and also lymph channels.

Most writers believe that the cells of the infiltrate may arise from the endothelial lining of the vessels but others attribute their origin to the adventitia of the perithelium, or the perivascular lymph spaces as mentioned by Philippson (197)

Bernhardt (19) Schwimmer (227) and others. The spindle cells are believed, by the majority to be of endothelial origin, others believe that they are derived from the adventitia, while still others regard them as connective tissue cells. Pick (196b) suggests that they may be caused by plasma cell transformation. Sternberg (248) believes that they arise from the muscularis of the adventitia, at least in some cases, and this opinion is shared by Gans (85) Fischl (76) and Perrin (195a) while a few others believe they originate from the round cells in the early perivascular infiltrate.

In one case Pautrier and Diss (191a) found that the cellular derivation was from the vascular neuromuscular annexes and Schwannian elements. They are convinced that the disease is a neurovascular dysgenesis and a pseudosarcoma. This opinion is supported by the work of Vigne and Pedat (266b) and Hudelo, *et al.* (122b) but is disputed by Radaeli (202) and by Tramontano and Fittipaldi (259) Dorffel (56) is convinced that the affection is primarily a disease of the reticuloendothelial system, including a disturbance in its monocytogenetic function, which at times may terminate in true malignancy but hesitates to call the disease a true reticuloendotheliosis. His opinion is based on the observation that the infiltration is perivascular lymphocytoid and reticular and is derived from the endothelial and adventitial cells and, also, on the presence of monocytosis and pigment. The conception that Kaposi's sarcoma is a disorder of the reticuloendothelial system, and that it may be more or less closely related to the "lymphoblastomas," is supported by the opinions of Nicolas and Favre (178) Puhr (201) Lane and Greenwood (143) Bluefarb and Webster (26c) and also by the fact that most parts of the reticuloendothelial system have been involved in numerous cases. The morphological resemblance to the neuroarterial glomus has been mentioned by Pautrier and Diss (191a) while the final suggestion, by Lang and Haslhofer (145) is that the condition is a systemic angiomatosis.

However it is the opinion of MacKee and Cipollaro (155b) that Kaposi's sarcoma is caused by an unknown systemic

agent which attacks the vascular apparatus, causing chronic hyperplastic inflammation and granuloma, and the histogenesis is compatible with, and indistinguishable from, that of a malignant new growth or neoplasm. The majority of investigators, including Dillard and Weidman (55) and Dorffel (56) agree that true sarcoma is produced, although this opinion is not held by all.

1 Neoplastic Theory Adherents of the theory of neoplasia are divided as to whether the tumor is benign or malignant and as to the origin and nature of the tumor cells.

It was Kaposi's (132b) contention that the disease was histologically a small round cell sarcoma, with the occasional occurrence of characteristic spindle cells. He thought it was a general disease because it began at the same time on both hands and feet. Unna (263) agreed with Kaposi and classified the disease with the sarcomata.

Others who have placed this disease in the sarcoma group include Jordan (129) Justus (130) Metscherski (168) Pollitzer (199a) Balzer *et al.* (10) Selhorst and Polano (229) Lieberthal (151b) and Hartzell (111)

Kuzenow (142) stated that we are dealing with a sarcomatous endoperithelioma and that the complicated genesis of these new formations is related to a disturbance in the balance between the endothelium and the perithelium of the capillary nests of the corium under the influence of an unknown factor In consequence of this, the endoperithelium exceeds the limits of normal change and builds an incomplete, though similar tumor tissue gradually involving more and more of the connective tissue elements in the tumor growth until, as in the older nodules, it finally forms a sarcoma like tumor

There are others who believe the disease is malignant, a vascular cancer or an angiosarcoma, i.e., one made up of connective tissue elements which apparently originated from the *adventitia of the vessels* *Development of new* blood vessels is also a marked feature Halle (105) found the process first developing as an angioma and later due to the proliferation

of the vascular perithelium, it took on the characteristics of an angiosarcoma. He considered it a peculiar form of sarcoma.

Bernhardt (19) and Hamdi and Besat (106) thought it was a malignant proliferation of perithelial cells. Radaeli (202) and Bertaccini (21b) believe the endothelial elements are the point of origin of neoplastic proliferation of angiomatous type. Sachs, *et al* (217a) stated that Kaposi's sarcoma is never a simple inflammatory process. New blood vessels and spindle cells are present in all sections, even those from pinhead sized lesions of one week's duration. They believe that from the beginning the disease is a potential sarcoma, that all lesions do not necessarily terminate as neoplasms, and that it may be considered a systemic angiosarcomatosis.

Aegerter and Peale (2) expressed the opinion that the disease is a vascular cancer angiosarcoma, and they regard the secondary visceral lesions as true metastases. This is contrary to the opinions of most observers who have studied Kaposi's sarcoma, for they regard the visceral involvement as, not metastatic, but of independent origin. Gonzales and Vidaurreta (91) are among investigators who have favored the theory of an angiosarcoma in this disease

Lever (150) summarizes the evidence against the concept of Kaposi's sarcoma as sarcoma and in favor of the autochthonous, rather than the metastatic origin of the lesions, as 1) the absence of a primary focus that progressively enlarges, 2) the appearance of widely separated lesions in crops, 3) the spontaneous regression of some lesions, and 4) the fact that histological examination may reveal very early stages of development in late-appearing lesions Occasionally however a lesion may undergo malignant degeneration and then grow as a true sarcoma and cause metastases.

It appears evident that the tendency to consider Kaposi's sarcoma as a true sarcoma is waning, and this theory finds but few advocates among the more recent investigators.

2. *Infectious Theory* Proponents of the infectious granuloma theory have in their favor the natural history of the disease which so frequently includes spontaneous regressions

which would be difficult to reconcile with malignant neoplasm (Cholsser and Ramsey: 40) To their disadvantage stands the fact that no etiological agent has ever been demonstrated despite extensive bacteriological work, and that transfer of the disease to animals has never been definitely established, although attempts have been made using every common laboratory animal and bird.

The existence of certain "predisposing causes and exciting factors is postulated by various writers to explain a malignant change in a previously benign growth, a neoplastic transformation on the part of an infectious granuloma or the development of reticuloendothelial hyperplasia, according to Cholsser and Ramsey (40) These include trauma, chilling or freezing of the affected parts, alcoholism, drug sensitivity erysipelas, cellulitis, arteriosclerosis, syphilis and acute infectious diseases, such as cholera, malaria, influenza and pneumonia.

The adherents of the infectious theory support their arguments mostly on the clinical behavior of the disease notably its preponderance in certain countries, its location and symmetry and the long duration and tendency to involution.

Philippson (197) believed in the infectious nature of the disease He stated the pathological changes are a new formation of capillaries and spindle cell tissue. The virus, he believes, enters the blood after an incubation period, where it may call forth either type of reaction, i.e the spindle cell or the hem- or lymph-angiomatous type. Sequeira (233b) considered the pathological reaction to be more the nature of an inflammatory reaction than a blastoma.

In examination of a dozen cases, Fraser (81a) could find no evidence of sarcoma. The earliest changes appeared to be in the capillaries. He noted a marked proliferation of the endothelium with an infiltration of mononuclear cells and fibroblasts. Cases have been reported in which true sarcoma developed in the course of the disease, but it does not follow that the original condition was a neoplasm It is well known that an inflammatory process may undergo changes that end

in a malignant process. In some of the reported cases sarcoma intervened, not on the Kaposi lesion, but apparently as an independent development.

Ewing (66b) believed that it is a granuloma, which in certain predisposed subjects, begins to take on a neoplastic property. The new growths in the viscera are probably not, he states, metastases, but arise from multiple foci which were originally inflammatory. The final tumor is the spindle cell sarcoma. He agreed that the late stages acquire neoplastic properties and give rise to a spindle cell sarcoma, but pointed out that the predominance of inflammatory signs indicated an infectious origin of granulomatous tissue with special involvement of the capillary endothelium. MacKee and Cipollaro (155b) concurred with this opinion. De Amicis (53) stated that the condition is an intermediate between an infection (granuloma) and a sarcoma. Homma (121) described a case of Kaposi's sarcoma in which the usual histologic picture was complicated by the presence of large numbers of giant cells, both of the foreign body and Langhans type. These cells were interpreted as indicating an inflammatory origin of Kaposi's sarcoma.

Stimulating processes, which ordinarily produce inflammatory effect may, on sufficiently prolonged application, induce malignancy according to Dillard and Weidman (55). They found fungus products in the mesenteric and gastrohepatic lymph nodes which bore some resemblance to Achorion Schoenleini, but there was no proof that these were the etiologic factor. On the basis of their studies, they believe the fungus they found is not the cause of the disease but believe it should be searched for in all cases which come to autopsy. They believe there is some general systemic influence which induces a dilatation of the lymph and blood vessels in the peripheral parts, with inflammatory agents entering later to produce the hyperplastic features of the stroma. They endeavored to produce similar lesions in rabbits by feeding them cultures of Achorion Schloenleini and injecting cultures intraperitoneally, but had no positive results.

The patient reported by Brunsting (30) was a 61 year old Negro who first developed small cutaneous tumors on both feet, nine years before. These progressed to involve the entire right sole and toe and the left instep. A diagnosis of blastomycosis, proved histologically had been made seven years previously. He believes this would leave the most plausible explanation of Kaposi's sarcoma developing on the background of an older infectious process.

Animal inoculations with tissue of Kaposi's sarcoma have produced lesions only in one instance. Justus (130) reported having injected into the back of a white mouse some emulsion of a rapidly growing area from a case of Kaposi's sarcoma. He later observed collections of new formed cells, especially around the arteries, in the lungs, the heart and liver. He succeeded, through *emulsifying the kidneys of the injected animal*, in transmitting this disease through five generations of mice, and the areas injected always showed the lesions characteristic of Kaposi's sarcoma. Civatte (41) believed that he had a positive inoculation in a chicken but later learned that angiomatous lesions occur in chickens at the site of inoculations of the most varied tumors. Santori (218) reported negative inoculation results in the anterior chamber of the eye of a guinea pig. Gilchrist and Ketron (87b) stated that results with an autogenous vaccine suggest that it is not autoinoculable. Grinspan (100) suggested a filtrable virus infection which in turn stimulates the reticuloendothelial system.

Despite the typical microscopic evolution of each Kaposi sarcoma lesion from an inflammation-like phase through a granulomatous phase into a true neoplasia, no bacteriological or viral agent has ever been isolated. Reinoculation of patients with their own tumor tissue by Pack (188a) and animal inoculations by Nesbitt, *et al* (176) and by Choisser and Ramsey (40) failed to induce tumors at the sites of inoculation. Cole and Crump (44) injected white rats, guinea pigs, young cats and rabbits with pieces of tissue emulsions, intraperitoneally but had no positive results. These, and other experiments, have somewhat nullified the concept that the tumor is an infectious granuloma.

3. *Systemic Vascular Disease.* The hypothesis accepted by some observers is that some agent, either chemical, bacterial or fungal, attacks the vascular mechanism, causing primarily inflammation and ectasia.

MacLeod (158) considers the process to be a proliferation of organizing connective tissue with vascular dilatation. He believes that, whatever the initial cause of the disease, it first attacks the blood vessel, causing a proliferation of the fixed cells in its zone of reaction. He states that it had more the appearance of proliferating connective tissue than a sarcoma and still less does it resemble a granuloma.

The disease begins as an angioma and the tumor stage results from proliferation of connective tissue and endothelium, according to Gilchrist and Ketron (87b) Their studies showed that the lesions originate in the skin, due to proliferation and dilatation of the blood capillaries, which are very frail at first and liable to rupture This is followed by a proliferation of the interstitial connective tissue and endothelium, which gradually obliterates the blood spaces forming solid tumors. In the early stages they resemble in some areas, young connective tissue in others, sarcomata. As the lesions grow older they assume a more fibrous aspect, and may undergo involution. Coexistent with the formation of the tumors, there is a sclerosis of the small arteries supplying them, causing a gradual decrease in the amount of blood. To this is due most likely their later evolution as well as involution.

Grzybowski (102) stated that the lesions are not granulomas but benign tumors. They are essentially angiomas, arising by proliferation of already existing blood vessels. Although endothelial proliferation occurs, these lesions cannot be classified with the endotheliomas because these are not the only cells which proliferate moreover the endothelial cells change their character in old lesions and become histiocytes or fibroblasts. The term perithelioma is also one to be avoided, he believes On the other hand, it is not a sarcoma, since the proliferating cells show no signs of malignancy but, on the contrary tend to undergo sclerosis Grzybowski concludes.

Nicolas and Favre (178) and Lang and Haslhofer (145) favor the theory that the disease is a systemic angiomatosis and Ramel (203) classified the condition as an endothelioma. Santori (218) expressed the opinion that the underlying disease is a congenital or acquired general debility of the vascular system. Sternberg (248) studied the nodules in the submucosa of the intestines in one case and found the new formation corresponded in every way to the surrounding muscular coat. He considered the disease, pathologically a combination of "lymph and hemangiectasien" associated with proliferation of the smooth muscle tissues. Serra (234) concluded that Kaposi's sarcoma is a "hemo-angio-endothelioma" and that the accompanying round cell proliferation is merely a secondary reactive phenomenon

Kaposi's sarcoma arises from capillary endothelium and is not a fibroblastic sarcoma, according to Fraser (81b) Highman (119b) stated that many investigators believe that fibroblasts are derived from endothelial ancestors and this was also his opinion. After careful histological studies, Meyers and Jacobson (167) concluded that the condition is probably one of multiple hemangiomatosis with a fibrosarcomatous change in the stroma of many of the tumor nodules.

Radaeli (202) and Bertaccini (21b) believed the endothelial elements were the point of origin of neoplastic proliferation of angiomatous type. It is the opinion of Bertaccini (21a) that the growth originates from the endothelium of the blood vessels. He bases this opinion on the similarity of the cells to endothelial cells and the transition forms between the masses of cells and fully formed blood vessels, and also on the tubular and concentric arrangement of the cells. He (21b) emphasized the abnormal appearance of the blood capillaries, which displayed thickness and hyalinosis of the walls of both in proximity to, and at a distance from, the lesions Along this same line is the explanation of Leigheb (148) in a case in which Kaposi's sarcoma apparently followed an erythema from arsphenamine

In describing a familial telangiectatic dysplasia of the Osler

type, Weber (273a) alluded to the possible analogy and association of the telangiectatic condition of the skin and mucous membranes of the nose and mouth with certain telangiectatic conditions of the stomach, intestines, kidneys and lungs. The telangiectasia in this disease he regarded as due to a congenital development dysplasia of the small vessels, potentially present at birth though often not manifesting itself until after puberty. The possibility that a malignant vascular growth originates from a localized debility in the vascular system is shown by a number of reports in the literature.

Coburn and Morgan (43) suggested that the condition is primarily a polyvasculitis, followed by a multi focal benign angiomatosis, and that the process may be similar to that which occurs in polyarteritis nodosa.

4 Derived from Nerve Tissue. As early as 1904 Perrin (194a) emphasized the nerve lesions in Kaposi's sarcoma. This disease was regarded by Pautrier and Diss (191a) to be a dysgenesis of the vessels and of their neuromuscular adnexa on the one hand, and of the nerves and their Schwannian elements, on the other. They stress the pain and the disturbances of local temperature observed and consider the vascular and nerve lesions as the anatomophysiological basis of the disease. Histologically they observed, not sarcoma, but organic elements in proliferation-vessels with a neuromuscular sleeve and a nerve network, and proliferation of cells of Schwann with formation of tactile corpuscles of Wagner Meissner type. They believe that Kaposi's sarcoma was to the vascular system what von Recklinghausen's disease is to the nervous system.

Hudelo, *et al.* (122b) presented a case which they called "Kaposi's telangiectatic pseudo-sarcomatosis." After detailed histologic studies they concluded that the lesion was not a sarcoma but an angiomatosis combined with a proliferation of the Schwann cells, that is, a dysembryoplastic lesion of the cutaneous vessels and of the adjacent Schwann elements similar to von Recklinghausen's disease. In a later report, Hudelo and Cailliau (122a) were of the opinion that the prolifera

tion of the neural cell is the essential and initial factor of the lesion, together with vascular neoformation arising from the proliferation of irritated endothelial cells. They believe the whole process to be due exclusively to the proliferation of sympathetic perivascular nerve fibers As a result of inflammation (perhaps due to infection) the nerve cells of the media and adventitia of normal vessels can first retrogress, then proliferate and become similar to the non-myelinated fibers of neighboring masses. They believe that such lesions are hyperplastic, but not neoplastic, and point out that the pseudosarcomatosis of Kaposi presents striking analogies to von Recklinghausen's disease They consider that the nerve elements in the vessel walls, irritated by the circulating toxins, *may initiate the tumor process in the vessels and connective* tissue which eventuates in Kaposi's sarcoma. However they pointed out, no traces, or insufficient traces, of the Wagner Meissner bodies, believed by Pautrier and Diss (191b) to be the starting point of this process, were found to bring this about and the normal nerve elements in the vessel walls may be capable of originating this tumor

It was pointed out by Lane and Greenwood (143) that some of the most competent pathologists in this country while agreeing with Masson's (163) original work on melanomas, do not consider the cases of either Pautrier and Diss (191a) or Hudelo *et al.* (122b) to have been proved. Becker and Thatcher (15b) despite the use of nerve stains, were unable to confirm these findings.

Anatomic changes in the central nervous system or trophic disturbances with changes in the peripheral nervous system, were found by Semenow (231) and Saphier (219) They believe there exists a relationship between Kaposi's sarcoma and the nervous system without pretending that the new growths of this condition are nerve tissue At two autopsies, Semenow found nodules in the skin stomach and intestines, liver pancreas and kidneys, and the spinal ganglion was filled with pigment and a swelling of the neuroglia nuclei and proliferation of the connective tissue in the peripheral nerves. He

believes the disease to be related to changes in the trophic nerves, induced, in some cases, by the action of cold and exposure. Saphier noted the disease spread along the peripheral nerves of the skin.

Nodl (180) believes that Kaposi's sarcoma is caused by a fundamental aberrant irritability of the nerves supplying the blood vessels. Interference with the normal circulation of the blood was considered responsible for the dilatation of the terminal vessels and the subsequent diapedesis. The later capillary proliferation was interpreted in agreement with Pautrier and Diss (191a) concept of neurogenic cellular elements.

5 As a Manifestation of Reticuloendothelial System Hyperplasia. Those who consider the condition merely a reticuloendothelial hyperplasia note the suggestive histological picture of the disease and the simultaneous occurrence of widely scattered lesions, as well as the not uncommon occurrence of other reticuloendothelial system diseases in patients having Kaposi's sarcoma. There are reports describing variation from mild lymphocytosis to frank lymphatic leukemia, mycosis fungoides and lymphosarcoma. Association with mycosis fungoides was described by Lane and Greenwood (143) Lapowski (146) and Winer (253 case 4) with Hodgkin's disease by Gilchrist and Ketron (87b) Goldschlag (90) Talbott (256) Greenstein and Conston (96) Osborne, *et al.* (187 case 7) McCarthy and Pack (153) Erf (66) and Wolf (287) with lymphosarcoma by McCarthy and Pack (153) Belloni (18) Higgins (118) and Bluefarb and Webster (26c) with lymphatic leukemia by Cole and Crump (44) Hufnagel and Dupont (123) Sachs and Gray (217b) and Fischer and Cohen (74) and with myeloid leukemia by Tedeschi, *et al.* (257) and Cuilleret and Gallet (51) This association was also noted by Ellis (61) Creppi and Bettoni (97) Kusnezow (142) and Warthin (270) The sites of the lesions further supports the hypothesis of reticuloendothelial origin, since the regions most richly supplied with these tissues are most frequently involved

On the basis of his studies, and corroborative evidence

found in the literature, Dorffel (56) believes that Kaposi's sarcoma is a disease of the reticuloendothelial system, a priori, not a true blastoma, but which may in some cases, become one after long continued irritation. The reticuloendothelial origin of the disease is also supported by Dalla Favera (52) Puhr (201) Lane and Greenwood (143) Dupont (58a) Dillard and Weidman (55) and others. That the products of blood degeneration might act as the endothelial stimulus has been suggested (55)

Bone marrow cells in a case of Kaposi's sarcoma were studied by Stitch, *et al* (251) who concluded that the cells were of reticuloendothelial origin. Becker and Thatcher (15b) also consider the disease as one of the reticuloendothelial system, with a disturbance in the monocytogenic function. They agree with Dorffel (56) that the presence of hemorrhage, proliferation of elements of the blood vessel walls, and cellular infiltration along with monocytosis justifies this theory The lymphocytoid cells of the infiltrate, which Dorffel considered reticuloendothelial cells, may form spindle cells giving a picture resembling lattice fibers, they state. The presence of lattice fibers throughout the infiltrate supports this theory Further evidence of generalized reticuloendothelial dysplasia is offered by Stats (246) and Tedeschi, *et al.* (257) who observed early microscopic deviations in the bone marrow lymph nodes, spleen and liver which were distinct from the primary cutaneous changes. McCarthy and Pack (153) also observed similar microscopic changes.

Puhr (201) explained the formation of blood vessels in the growth by fusion and subsequent evacuation of cells in which he recognized all the functional and morphological characteristics of the reticuloendothelial cells. Greppi and Bettoni (97) reached a similar conclusion in studying an unusual case of Kaposi's sarcoma with extensive visceral manifestations and concomitant hemolytic splenomegaly The involvement of the reticuloendothelial system in this case, they believe, had manifested itself in the splenic area with an exaggeration of the hemocatheretic function proper to this organ, while else

where it had given rise to a neoplastic growth with the characteristics of Kaposi's sarcoma. Guccione (104) Flarer (77) Choisser and Ramsey (40) and Goldsmith (89) also classify Kaposi's sarcoma among the diseases of the reticuloendothelial system.

Tedeschi, *et al.* (257) state that Kaposi's sarcoma is systemic in nature and likely to involve independently and in an unpredictable manner simultaneously or successively the skin and the internal organs and that it is characterized from the histologic standpoint by a great variety of patterns inherent to the multiple developmental potentialities of the basic unit of growth, the reticulum cell.

In a detailed histologic report, Dorffel (56) described the endothelial cells which originally line the sinuses breaking away to form solid masses and finally becoming spindled to resemble fibroblasts. He found that the cellular infiltrate displays a surprising richness of forms to which the term lymphocytoid, as used by Marchand (159) is most applicable. He believes that these cells arise from the reticuloendothelial system and gives the following reasons: 1) the cells are distributed almost entirely about the blood vessels, 2) the vessel wall elements are swollen, and there is definite evidence of proliferation, 3) they form a reticulum, present also in some places in the vessel walls themselves, thus allowing "hemorrhages by dissection (Herzog 116) to occur 4) there is a multiplicity of cell forms with many transitional changes, as they are differentiated from the central vessel to the periphery of the nodule, and 5) large endothelial cells are found connected to the intima of the vessel, but are just on the verge of entering the systemic circulation and becoming transitional cells, or are already definitely monocytes. These transitional cells and monocytes are found also in the tissues as well as in the circulating blood.

The monocytes represent the third system of blood production in the body the other two being lymphogeneous and myelogenous, according to Schilling (222) The monocytes, he is convinced, arise from the endothelial cells. Dorffel (56)

d Ramsey 40, Dorffel 56, and Pautrier and Diss 198a).

Other Theories. De Amicis (53) who, in 1897 had examined more cases of Kaposi's sarcoma than any other investigator, believed that the relation of the disease to sarcoma was close and the primary lesion must be considered a type similar to itself lying between a granuloma and a sarcoma. Bocker and Thatcher (15b) studied embryonal mesenchymal cells in tissue cultures and found many histiocytes which differed greatly from the fusiform cells. The latter were not fibroblasts and they did not act as malignant cells do. They stated that there is a unique type of cell reaction of the embryonic cells in Kaposi's sarcoma. The lymphocytoid cells of Marchand are stimulated by some unknown agent which may produce a benign neoplasm. They believe that Kaposi's sarcoma is a benign neoplasm. In some instances it goes on to malignant hyperplasia, just as myofibroma of the uterus occasionally goes on to the formation of sarcoma. They believe that the exact classification of the tumor is too hazardous to attempt, but it is probably a benign neoplasm with a multicentric origin characterized by a vascular proliferation and hyperplasia of spindle cells arising in the perithelial tissue, without designating the particular cell of the several types constituting the perithelium. The most logical explanation of Kaposi's sarcoma, in their opinion, is that it is a multicentric benign neoplasm originating in the perithelial tissue from embryonic mesenchymal cells (lymphocytoid cells of Marchand) which results in a type of cell growth unique for this disease. After a period of years, the cells may undergo malignant degeneration producing true sarcoma, resulting in metastasis and death. True metastasis is rare although the spindle cells which constitute the tumor may become malignant and give rise to a true sarcoma as in Bocker and Thatcher's (15b case 2) case and as reported by Ewing (68b) Dillard and Weidman (55) Dorffel (56) and MacKee and Cipollaro (155b)

The fibroblast determines the growth behavior of each of the phases by which Kaposi's sarcoma may be characterized, according to Symmers (254a) 1) the fibroblast may produce

where it had given rise to a neoplastic growth with the characteristics of Kaposi's sarcoma. Guccione (104) Flarer (77) Cholzner and Ramsey (40) and Goldsmith (89) also classify Kaposi's sarcoma among the diseases of the reticuloendothelial system.

Tedeschi, *et al.* (257) state that Kaposi's sarcoma "is systemic in nature and likely to involve independently and in an unpredictable manner simultaneously or successively the skin and the internal organs and that it is characterized from the histologic standpoint by a great variety of patterns inherent to the multiple developmental potentialities of the basic unit of growth, the reticulum cell.

In a detailed histologic report, Dorffel (56) described the endothelial cells which originally line the sinuses breaking away to form solid masses and finally becoming spindled to resemble fibroblasts. He found that the cellular infiltrate displays a surprising richness of forms to which the term lymphocytoid, as used by Marchand (159) is most applicable. He believes that these cells arise from the reticuloendothelial system and gives the following reasons 1) the cells are distributed almost entirely about the blood vessels, 2) the vessel wall elements are swollen, and there is definite evidence of proliferation, 3) they form a reticulum, present also in some places in the vessel walls themselves, thus allowing "hemorrhages by dissection (Herzog 116) to occur 4) there is a multiplicity of cell forms with many transitional changes, as they are differentiated from the central vessel to the periphery of the nodule, and 5) large endothelial cells are found connected to the intima of the vessel, but are just on the verge of entering the systemic circulation and becoming transitional cells, or are already definitely monocytes. These transitional cells and monocytes are found also in the tissues as well as in the circulating blood.

The monocytes represent the third system of blood production in the body the other two being lymphogeneous and myelogenous, according to Schilling (222) The monocytes, he is convinced, arise from the endothelial cells Dorffel (56)

found evidence of endothelial proliferation with monocytes in the tissues and monocytes in the differential blood smear In this manner Fischer Wassel's (75) requirement is fulfilled, since he states that when a tumor has originated from proliferating endothelial cells, monocytosis should be present. The presence of gitterfasern is perhaps further evidence of the involvement of the reticuloendothelial system, since they are usually found, as described by Way and Klovekorn (272) and others, and confirmed by Dorffel (56) as demonstrated so clearly in the early angiomatous stage of Kaposi's sarcoma. Gitterfasern are also found normally in the liver (Rossle,211) where cells of the reticuloendothelial system are so numerous

Another manifestation is found in the presence of the nodules of sinus-like spaces lined by endothelial cells containing fine pigment granules and strongly resembling similar cells and spaces in the spleen, according to Dorffel (56) He believes that the cell type involved basically is the pluripotent cell of the reticuloendothelial system which, owing to its various developmental potentialities, is able to give rise to complex and unpredictable structures. He concludes that Kaposi's sarcoma is a disease of the reticuloendothelial system, including a disturbance of its monocytogenetic function, which at times may terminate in true malignancy He supports this belief with the following points of evidence 1) the vascular system throughout the body is the site of definite clinical changes such as ectasia, varicosities and purpuric lesions 2) nodules may be found distributed along the vessels and adherent to the vessels, 3) microscopically newly formed capillaries and a polymorphous cellular infiltrate are found, the cells of which arise from the reticuloendothelial system (lymphocytoid cells) 4) the monocyte system is affected as evidenced by an increased number of monocytes in the tissues and monocytosis in the differential blood smear and 5) the presence of gitterfasern does not permit too definite conclusions on this point.

Walzer (288a) stated that many cases of Kaposi's sarcoma end in sarcoma or some other form of "lymphoblastoma and

there is probably a definite relationship between these diseases. The conception of the systemic nature of Kaposi's sarcoma and its relation to "lymphoblastoma" and reticuloendothelioma have been recently emphasized.

Dupont (58a) noted the fusiform cells which constituted most of the tumor mass, their phagocytic properties and their ability to form rosettes of reticulum fibers, and he believed that only one cell, the histiocyte, is capable of such activity. He proposed the name "angioreticulose." It was suggested by Choisser and Ramsey (40) that all the multiple cell types *found might arise from the reticuloendothelial system* and, therefore, thought the condition might be designated angio-reticuloendothelioma." Grinspan (100) suggested a systemic reticuloendothelial hyperplasia due to a virus infection and stated that the disease should rightly be called angio-reticulo-endotheliosis of Kaposi.

The reticuloendothelial theory was disputed by Ewing (68b) who believed that Kaposi's sarcoma was a systemic disease in which a more specific structure, such as the neuro-myoarterial glomus was involved. Isren (139) doubted that the cells primarily involved are the reticuloendothelial cells and stated that the only substantial points in favor of this origin is the presence of cells provided with phagocytic power in the newly formed nodules.

According to McCarthy and Pack (153) solution of the problem of pathogenesis is not imminent and possibly will not materialize until tissue cultures of early Kaposi's tumors are investigated. They believe that, although a start has been made in this direction, the results are not conclusive and tissue cultures would seem to implicate primitive mesenchymal tissue as the origin.

It is necessary to determine which body tissues are capable of giving rise to the numerous and diverse structures observed in newly formed blood vessels, including endothelium and adventitial connective tissue, embryonic spindle cells, lymphoid elements and well organized reticulum. Only from the reticuloendothelial system could all these types be derived (Chois-

ser and Ramsey 40 Dorffel 56, and Pautrier and Diss 189a)

6 *Other Theories.* De Amicis (53) who, in 1897 had examined more cases of Kaposi's sarcoma than any other investigator believed that the relation of the disease to sarcoma was a close one, and the primary lesion must be considered a type peculiar to itself, lying between a granuloma and a sarcoma.

Becker and Thatcher (15b) studied embryonal mesenchymal cells in tissue cultures and found many histiocytes which differed greatly from the fusiform cells. The latter were not fibroblasts, and they did not act as malignant cells do. They stated that there is a unique type of cell reaction of the embryonic cells in Kaposi's sarcoma. The lymphocytoid cells of Marchand are stimulated by some unknown agent which may produce a benign neoplasm They believe that Kaposi's sarcoma is a benign neoplasm. In some instances it goes on to malignant hyperplasia, just as myofibroma of the uterus occasionally goes on to the formation of sarcoma. They believe that the exact classification of the tumor is too hazardous to attempt, but it is probably a benign neoplasm with a multicentric origin, characterized by a vascular proliferation and hyperplasia of spindle cells, arising in the perithelial tissue, without designating the particular cell of the several types constituting the perithelium. The most logical explanation of Kaposi's sarcoma, in their opinion, is that it is a multicentric benign neoplasm originating in the perithelial tissue from embryonic mesenchymal cells (lymphocytoid cells of Marchand) which results in a type of cell growth unique for this disease After a period of years the cells may undergo malignant degeneration, producing true sarcoma, resulting in metastasis and death. True metastasis is rare although the spindle cells which constitute the tumor may become malignant and give rise to a true sarcoma as in Becker and Thatcher's (15b case 2) case and as reported by Ewing (68b) Dillard and Weidman (55) Dorffel (56) and MacKee and Cipollaro (155b)

The fibroblast determines the growth behavior of each of the phases by which Kaposi's sarcoma may be characterized, according to Symmers (254a) 1) the fibroblast may produce

young argentophilic collagenous fibrils which reenforce the mature collagenous bundles in such a manner as to aid in the process of healing; 2) the fibroblast may maintain a low almost stagnant capacity for growth over a long number of years, and 3) the fibroblast may suddenly assume active malignant properties and terminate life by widespread destruction of tissues through the process of metastasis. Histologic study of the younger growths, according to Symmers, shows that from the onset two opposing factors are operative one tending to bring about replacement of the nodules by the production of collagenous fibrils, the other tending to maintain the capacity of the nodule to grow but at an extremely slow rate. Excluding such incidental features as hemorrhagic extravasations between the fibroblasts and deposits of pigment following destruction of the red blood cells, the histologic appearance of the well developed growths in Kaposi's sarcoma is scarcely to be distinguished from that of spindle cell sarcoma. Whereas the spindle cell sarcoma almost always grows rapidly and without restraint, the progress of the spindle cell growths of Kaposi's sarcoma is retarded almost to the point of stagnation. In other words, the growths of Kaposi's sarcoma are histologically malignant but clinically benign. The process of spontaneous regression and healing in the cutaneous lesions of Kaposi's sarcoma, Symmers continued, is probably instituted by the sudden release, traumatic or otherwise, of large numbers of red blood cells followed by injury to or destruction of large neighboring fibroblasts and finally by connective tissue replacement The smaller and presumably younger nodules are permeated by a complex network of argentophilic reticulum which serves primarily as a mechanical support for the fibroblasts.

Pick (198a) believed that spindle cell tissue had its origin in the plasma cells which accompany the blood vessels. These plasma cells, he stated, are capable of developing into endothelial-like cells which, after exhausted energy ended in fibrous tissue He classed the disease with sarcoid growths.

Histologic studies at autopsy were done by Dalla Favera

(52) in two cases having nodules in the trachea, bronchi, lungs, stomach and intestines, lymph nodes and skin. He believed that spindle cells originated in the connective tissue and, in the cutaneous lesions, was able to trace the gradual change of the spindle cell bundles into the collagenous tissue of the corium and to demonstrate fibrils in the spindle cells. In the lungs, the small pinhead sized nodules had developed almost entirely around the small bronchi and the accompanying branches of the pulmonary arteries. He was of the opinion that the exciting cause of the disease might call forth both types of reaction spontaneously, i.e., the new formation of capillaries and the spindle cell growth. The quantitative reaction between the two was variable but the angiomatous tissue became less pronounced as the lesions grew older.

Belloni (18) considers the disease a hyperplastic mesenchymal one with multiple, systematically arranged foci, presenting the following characteristics: A. Pronounced poikiloblastic tendency, i.e., a capacity for various types of anatomo-function differentiation (1. Angioblastic, predominating in the regions of the cutaneous and intestinal lesions, 2. Fibroblastic, causing the cicatricial regression of the lesions, 3. Macrophagicopexic and 4. Hematopoietic- lympho-monocytic type of cells, Flarer's cells) and B. The possibility of a leukemic and neoplastic development.

Although a solution of the etiology is far from settled, recent advances in the general field of carcinogenesis make it plausible now to suspect some systemic carcinogen acting on the vascular tissues as a possible agent, according to McCarthy and Pack (153). Such a hypothesis, they believe, would more logically explain the distinctive tendency of Kaposi's sarcoma to involve the legs bilaterally and symmetrically, and ultimately manifest itself throughout the viscera with multiple adjoining tumors in the inflammatory, granulomatous and sarcomatous phase and resembling multicentric foci rather than metastases. It is now possible to induce similar angiosarcomas in animals with injections of chemical carcinogens.

Andervont (5) and White and Stewart (277) have induced

numerous benign and malignant angiomatous tumors, several of which acted as primary tumors of multicentric origin, with the administration of azo compounds and hydrocarbons to mice. Andervont also determined that female mice were far more susceptible to such induction than male mice, and clearly established the influence of sex hormones by markedly reducing induction with castration and testosterone pellet implants. Further evidence of a systemic factor in humans is the early proliferative changes of Kaposi's sarcoma in the liver spleen and lymph nodes which are far removed from the gross and obvious sarcomatous nodules in the skin, as described by Stats (246) and Tedeschi, *et al.* (257)

There are probably other etiological factors such as sex hormones, since the incidence of Kaposi's sarcoma is high in men. Among 1,058 patients with hemangioma, reviewed by Watson and McCarthy (271) 65 per cent were women. They also noted a definite growth stimulation of angiomas at the onset of pregnancy and the menarche. Many women with Kaposi's sarcoma have manifested its most bizarre forms. A fulminating case described by Symmers (253a) was an Italian woman who survived for only 34 days after the cutaneous lesions appeared.

A 53 year old woman who developed an allergic arteritis following sensitivity to penicillin was described by McGinn, *et al* (154) She then developed a vascular (Kaposi's) sarcoma. Coburn and Morgan (43) suggested that this condition is primarily a polyvasculitis, followed by multi-focal benign angiomatosis. They also suggested that the process may be similar to that which occurs in periarteritis nodosa.

B. Morbid Anatomy

Kren (139) states, "The cardinal changes that characterize Kaposi's sarcoma histologically consist of new growth and ectasia of capillaries, hemorrhage and proliferation of connective tissue The vascular changes concern primarily the blood vessels and only to a lesser extent, the lymph vascular system.

Pigmentation develops from hemorrhage, and reaction processes occur about vascular and connective tissue, finally reaching the stage of involution and healing with lesions resembling scar tissue. Nevertheless, the histologic pictures are very different, depending on whether vascular or fibrous changes predominate in the tissue and whether circumscribed or diffuse cellular proliferation develops."

This brief introduction presents the essential features present in Kaposi's sarcoma. It is important when studying the pathology that lesions of various ages be carefully examined, for not only do lesions vary in different cases, but they also vary in individual cases. Single sections may be angiomatous, granulomatous or neoplastic, or they may show combinations of any of these histological features.

The cutis is the site of development of the lesions. The epidermis plays no primary role in the process and the epidermal changes such as thinning, acanthosis, hyperkeratosis or breaking down are all secondary to the advancing process. The first change consists of capillary dilatation and capillary budding. Dorffel (56) and Van Cleve and Hellwig (265) however stated that the first pathologic change is the occurrence of hemorrhage in the cutis from one or many vessels at different depths in the cutis. They believe the hemorrhage is the initial, pathologic feature of the disease, together with the proliferation of the vessel wall elements and cellular infiltration. The vessels in the vicinity show engorgement and some dilatation, and there is already present a deposit of iron pigment Clinically at this stage if the hemorrhage is deep, nothing is found grossly other than a faint hemorrhagic macule. If the hemorrhage is more superficial, localized areas of blood extravasation in the skin, or even a diffuse purpura-like eruption, may be observed. This stage must be one of short duration because in most cases evidence of cellular infiltration is already present at the time of examination. Dorffel (56) believes that infiltration of the round cells occurs almost simultaneously with the hemorrhage

On the other hand, Sachs, *et al.* (217a) believe that the



19. Angiomatous, granulomatous and neoplastic stages present in one histologic section.

20. Infiltrate consisting of spindle cells, hemorrhage, pigment and newly formed capillaries.

hemorrhage is secondary rather than primary and is the result of erythrocytes wandering into the surrounding tissue from imperfectly formed new vessels or through ruptured or damaged vessels. The proliferation of thin walled vessels is thus to be considered as the primary process and hemorrhage is secondary. The newly formed ectatic capillaries appear to be angiomas and these vessels lie in a cellular stroma composed of lymphocytes, plasma cells, wandering connective tissue cells, angioblasts and mast cells. Between the bundles of capillaries there are delicate, spindle-like fibroblasts. Depending on which of the above features predominate, the section may appear to be angiomatous, fibrous, granulomatous, inflammatory or highly malignant sarcoma.

Hansson (108) states that there is agreement that the main distinctive features of both tumors and infiltrations is the new growth and dilatation of capillaries. Many of the nests are to a large extent composed of such capillaries. Besides this capillary proliferation, there also occurs, almost without exception, hemorrhages and deposits of blood pigment in the surrounding tissue. Philippson (197) Sellei (230) and Pick (198a) have also reported dilatation of the lymph capillaries. Because of the increased vascularity the new nests sometimes resemble inflammatory granulation tissue. In addition to the newly formed capillaries, there is often a fair amount of fusocellular polymorphism present, which gives rise to sarcoma like structures, especially in lesions of long standing.

Hemorrhages are probably responsible for nutritional disturbances which sometimes result in necrosis and cicatrization of both tumors and infiltrations. Spontaneous healing of the single nests may take place in this manner as noted by Hansson (108). Sclerosis of the nests occurs following radiation therapy. He examined the tumors histologically before and after radiation in three cases, and in all the sclerotic condition was very distinct.

As the infiltrate decreases the vessel wall cells reveal their ability to form new blood vessels, according to Dorffel (58). However this inability has been impaired, as evidenced by



1. Capillary dilatation and budding.
2. Engorgement of blood vessels and deposition of iron pigment.

the presence of incompletely formed blood vessels. In these new blood vessels there is also proliferation of the vessel wall elements.

MacKee and Cipollaro (155b) cite Satenstein (220a) regarding the three pathological processes recognized inflammatory granulomatous and neoplastic. By this he means that the very early stage resembles inflammation and may be so classified. Later stages may resemble chronic hyperplastic inflammation, granuloma or a new growth. Very often these processes overlap and produce a borderline or mixed picture

When the inflammatory process predominates, the cardinal features are:

1. Dilatation of blood vessels and lymphatics
2. Perivascular infiltration of mixed cells—round cells, connective tissue cells and some plasma cells
3. Edema, hemorrhage and iron-containing pigment

When the granulomatous element is accentuated, the predominating features are

1. Proliferation of connective tissue with young nucleated cells predominating and perivascular infiltration of mixed cells
2. Edema, hemorrhage and iron pigment

When the neoplastic feature predominates, the picture varies with the elements involved:

1. When the changes are primarily vascular the picture may be that of angioma or may resemble granulation tissue or granuloma
2. When the lymphatics are involved, the picture may suggest lymphangioma or a mixture of angioma and lymphangioma
3. When the connective tissue proliferation predominates, fibroma, angiofibroma, angiosarcoma, or spindle cell sarcoma may be suggested.

The three stages of development of Kaposi's sarcoma are described by Hamdi and Resat (106) In the first stage, the

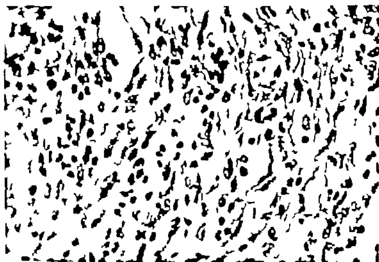




23. Newly formed ectatic capillaries.
24. Inflammatory stage of Kaposi's sarcoma.



25. Inflammatory stage of Kaposi's sarcoma.
26. Granulomatous stage of Kaposi's sarcoma.





27 Gr[illegible]lomatous stage of Kaposi sarcoma (higher magnification of Figure 28)

28 [illegible] stage of Kaposi sarcoma. Low power magnification.



29. Fibroblasts and vascular proliferation. Perivascular lymphocytic infiltration.

30. Diffuse vasculitis. Vascular proliferation. Perivascular lymphocytic infiltration.



31 Fibroblasts.
32. Periglandular infiltrate.

early growths are faintly visible to the naked eye and barely palpable. Microscopically the blood vessels of the skin are surrounded by zones of cells rich in protoplasm resembling epitheloid cells. Often, these cells show a complete series of transitional forms, indicating their transformation into connective tissue. Many of the blood vessels break up into a fine network of ramifying capillaries composed solely of a wall of endothelium. The neoplasm in this stage is similar to fibroangioma In the second stage, the growths are clinically prominent as elevated red or purple intradermic tumors. Histologically they are poorly delimited growths composed of aggregates of fusiform cells with a perivascular distribution. The blood vessels are numerous and vary in size. Many red blood cells are to be found in the interstitial tissues. In the third stage, the older growths assume a dark brown or bluish color depending on the extent of hemoglobin destruction. In some of the more advanced cases, the cellular aggregates are found about the terminations of the peripheral nerves, the sweat glands, the pilomotor muscles and hair roots, and even in the subcutaneous adipose tissue. The fact that these cellular foci rarely fuse connotes an independent and spontaneous origin for each of them, for a general sarcomatosis of this type is not produced by the emigration of cells.

Before any of the features show pronounced proliferation, the findings are those described in the inflammatory stage, according to Sachs, *et al.* (217a) The blood vessels of the upper and mid cutis are dilated, increased in number frequently filled with blood elements and arranged in groups or scattered diffusely throughout the cutis. The endothelial cells are swollen and have large vesicular nuclei projecting into the lumen. These nuclei may be round and somewhat hyperchromatic rather than oval and vesicular Instead of being elongated, the cells may appear rectangular (cross-section of the endothelial cell) and resemble somewhat the embryonic plasma cell of the young granulation tissue The lymph vessels and spaces are prominent. The cellular infiltration is sparse, perivascular as well as diffuse and composed

of small round and wandering connective tissue cells, angioblasts and some spindle cells. Plasma and mast cells are occasionally seen. There is no hyperplasia of connective tissue and no changes in the elastic tissue. Erythrocytes or intracellular or extracellular granules of hemosiderin, indicates hemorrhage. As the process develops (late stage: granulomatous or neoplastic) they continue different pictures are noted as vascular connective tissue or cellular hyperplasia becomes prominent. With the proliferation of vessels, the appearance is that of angioma. Vascular and cellular hyperplasia may mimic granulomas, glomus tumor and granuloma pyogenicum. If the vessels are associated with numerous angioblasts, Kaposi's sarcoma may simulate angiosarcoma, perithelioma or endothelioma. In some of their sections, there were areas that in no way differed from glomus tumor Where spindle cell proliferation is the characteristic feature, the result is a spindle cell sarcoma. Masses of cells extend in all directions, and at times show mitotic figures; other cellular elements, as well as vascular and connective tissue hyperplasia, are not prominent. If the connective tissue, rather than cellular elements, is increased, the picture suggests an angiofibroma. The growth of fibrous tissue is never extensive and frequently separates the process into lobules. Frequently areas characteristic of various dermatoses are seen in the same section. Vascular hyperplasia, hemorrhage angioblasts and spindle cells are found throughout the evolution of the disease except perhaps in the development of spindle cell sarcoma, where the proliferation of spindle cells overshadows all other features.

As the lesions become older according to Dorffel (58) the lymphocytoid elements begin to play a lesser part and the angiomatous features become more prominent. The lymphocytoid cells, however may later go on to form spindle-like cells, to give the picture of sarcoma-like lesions, which he believes represents the final stage of the process. He has seen such a transition even in the earliest lesion, since he studied the polymorphism of the cells from the vessel to the periphery of the nodule where they assume the spindle-like form and

produce, in some places, thin collagen fibers. At times the angiomatous features are so typical that a diagnosis of cavernous hemangioma would be justified. Again, in cases in which the activity of the reticuloendothelial system is more marked, the angiomatous features are present along with sarcoma like features with mitotic figures, and the diagnosis suggested would be angiosarcoma. In such cases of increased activity he found the previously described, but so important, poly morphism of the cellular infiltrate; the whole picture representing all stages of development of the process in the lesion.

Dorffel (56) believes that the relationship between the presence or absence of gitterfasern and elastic fibers is of interest. In the earliest lesion, the elastic tissue is injured, or perhaps even completely destroyed throughout the whole cutis, even including parts of the cutis where the actual lesion is not present At this time, gitterfasern are very prominent. As the lesion develops and the angiomatous picture appears, the gitterfasern remain a striking feature, while the elastic tissue, although completely destroyed within the tumor may be found less severely injured in the adjacent tissue. In the still later sarcoma-like stage there are very few gitterfasern to be found, and still no elastic tissue is present in the tumors. There is, however an almost normal elastica in the tissues near the tumors.

The collagen fibers in the earliest lesions may be the site of degenerative changes of edema, homogenization and slight vacuolization, in some places, according to Dorffel (56) With the van Gieson stain, bright pink, newly formed collagen fibers make up the stroma of the tumorous structure, while the fibers in the adjacent tissue seem normal. In the later sar coma like stage with the extremely cellular make-up of the tumor few collagen fibers are found, whereas in the surround ing tissues the collagen fibers show regressive changes, which ultimately will be supplanted by new granulation tissue. From this description, one must be struck by the great powers possessed by the reticuloendothelial cells to form new cells other than those that they produce under normal conditions. He



33. Incr ase of retic lum fibers in granulomatous stage (gitter f stain)

34. P l morphism of cellular infiltrate

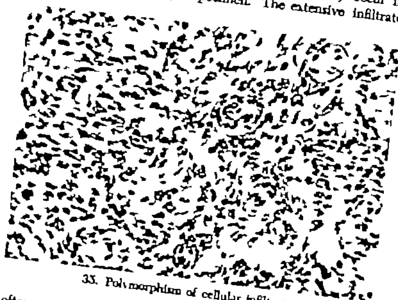
believes that cells, to have such power can be only "embryonal" in the sense that they are undifferentiated and remain so until need for their differentiation arises, as mentioned by Herzog (116) Marchand (159) Maximow (164a) and others.

Large amounts of iron pigment are present in the cutis which may be intracellular as within vessel wall cells or in the cells of the infiltrate, according to Dorffel (56) However much of the pigment is extracellular giving the cutis a strongly positive iron (hemosiderin) reaction throughout. The infiltrate occurs in a diffuse form, with a tendency to be perivascular It consists mostly of plasma cells, fixed wandering cells and cells of the lymphocytic group Endothelial cells, in direct relation to blood vessels or entirely apart from them, are seen grouped in the infiltrate, proliferative changes being constant. Mast cells, lymphoblasts and transitional cells are also found in small numbers scattered throughout the infiltrate. Elastic fibers are partly or completely destroyed, the collagen fibers are usually involved, but to only a slight degree and the fat and nerve stains show no pathological changes. Extension of the lesions is along the vessels and by peripheral extension around the vessels.

Mackee and Cipollaro (155b) reported that pigment granules could occasionally be seen in the cells. They did not observe melanin although this has been reported by Hamdi and Resat (108) Rottman (214) Masson (162) and a few others. Gans (85) and Kren (139) believe that in such instances the diagnosis was erroneous, the disease being associated with leukemia or mycosis fungoides, or that the presence of the pigment was due to arsenic therapy There is almost universal absence of melanin in Kaposi's sarcoma, except in the epidermis.

The late changes are more numerous and varied, according to Mackee and Cipollaro (155b) The infiltrate spreads and forms masses of nodules, consisting of cells of various types small round cells, plasma cells, connective tissue cells, spindle cells and, occasionally mast cells and giant cells. The giant

cells appear to be of the foreign body type. The formation of new capillaries is a prominent feature. These are often numerous, ectatic and even cavernous. They give rise to hemorrhages and subsequent pigmentary deposits. The connective tissue becomes hyperplastic and often degenerated. Elastic tissue and the appendages disappear. As they noted, any of these features may predominate, or many of them may occur in various parts of a single specimen. The extensive infiltrate



33. Polymorphism of cellular infiltrate

often consists mostly of spindle cells with whorl formation and numerous mitotic figures. Involution is indicated by a large number of plasma cells, poor staining properties, vacuolization and other evidence of degeneration, together with fibrotic transformation, producing the appearance of chronic granulation tissue with ultimate regeneration, fibrosis or cicatrization. All this has been reported in older lesions by practically all investigators, but Dorffel (56) noted evidence of beginning involution even in very early lesions. He found that signs of involution may be suggested even in early

papules, but in later stages are quite pronounced. He described these signs as: poorly staining cells, vacuolization of nuclei, cytoplasm or both, and some fragmentation and disintegration of nuclei. Rarely small areas of myxomatous degeneration could be found. Kaposi (132b) suggested that fibrin appeared in the large vessels and resulted in clotting of red blood cells, thus causing involution of the older tumors, and this was corroborated by Dorffel. Small amounts of fibrin were present in some vessels in early as well as in late tumors, even when signs of involution were absent, but in such minimal amounts that it was scarcely conceivable that this could result in involution of the tumors. In conjunction with these degenerative changes, fibrous transformation of parts of the tumor with the appearance of chronic granulation tissue, was found. Perhaps this granulation tissue is evidence of the final function of the vessel wall cells that have been able to retain their normal capacity to form regeneration tissue in the body Dorffel concludes.

There is much difference of opinion regarding the genesis of spindle cells. Some (Sequeira 233b) attribute their presence to proliferating endothelial cells. However most investigators, including Dalla Favera (52) believe they originate from cells of the connective tissue. Sternberg (248) considers that these cells arise from smooth muscle fibers. Spindle cells are found only in spindle cell sarcoma, or in a process which may eventuate in such a sarcoma, according to Sachs, *et al* (217a) They are led to believe that the sarcomatous process is not due to a simple accumulation of spindle cells from the parent cells, but may depend on proliferation of these cells from other spindle cells. The numerous mitotic figures found in these cells would substantiate this view The cytoplasm of the spindle cells is scant and the cell tapers to a point at either end the nucleus is narrow oval and vesicular with loosely arranged and lightly stained chromatin. The length of the cell is approximately twice that of the nucleus. They doubt that this cell plays any role in the production of collagen. Many different types of cells, even epithelial cells, may

have spindle shapes, such cells should be referred to, not as spindle cells, but as spindle-shaped cells. They state that the relation of the fibroblast to the spindle cell is unknown. Contrary to the opinion of many they believe that the two cells *are different in morphology in function and, probably in derivation* The fibroblast is much larger in all dimensions and often has fiberlike projections extending from the tapering points. It has an oval vesicular nucleus which is larger and greater in diameter than the nucleus of the spindle cell. Unlike the spindle cell, the fibroblast does form collagen. The angioblast is believed to arise from the endothelial cells and is sometimes referred to as an endotheloid cell. Maximow and Bloom (162b) believed that the term angioblast should not be used However while the term endothelioid cell may be acceptable, Sachs, *et al.* prefer to retain the name angioblast because these cells are said to give rise to new vessels and because the mature cell usually does not resemble an endothelial cell. *The angioblast has a round nucleus approximately* one and one-half to two times the size of the nucleus of a lymphocyte It stains deeply but the chromatin does not appear as a solid mass. As a rule, little or no cytoplasm is observed. However a few of their sections showed the angioblasts with considerable cytoplasm. This is not unlike the polyhedral, pavement like appearance of endothelial cells when the flat surface is examined.

In summary Kaposi's sarcoma is often classified as "early or late and as inflammatory granulomatous or neoplastic. Such division is not entirely accurate for the pathologic picture does not always coincide with the duration of the process. While such a classification is arbitrary it is convenient and often helps to correlate the pathological picture with the clinical picture While investigators disagree on the pathogenesis, there is almost complete accord as to the characteristic *histological features. The histological structure consists* of the infiltrate, numerous spindle shaped cells, hemorrhage, pigment and newly formed capillaries and blood spaces.

V

SYMPTOMS

A. Subjective Symptoms

SUBJECTIVE symptoms caused by the cutaneous manifestations of Kaposi's sarcoma are usually slight or absent. Patients having numerous large lesions on the extremities, particularly those with marked edema, may have local discomfort and interference with, or even loss of function of these parts. Visceral involvement may cause hemorrhage, diarrhea and other constitutional symptoms, including emaciation. There is occasionally hemorrhage from the cutaneous orifices, particularly the nose, mouth and throat.

There may be itching and burning, as described by Meyers and Jacobson (167). Two of Symmers' (254a: cases 4 and 5) patients had intense and persistent pruritus of the affected areas and Dorffel (56) described pruritus and edema which preceded the eruption. This intense pruritus is very unusual in Kaposi's sarcoma and, as a rule, is not a major complaint. As a result of the pruritus, trauma may cause bleeding of the lesions.

Occasionally there is complaint of pain. This is usually due to the localization of nodules on the feet, which causes pain on walking. This symptom was present in four patients reported by Hansson (108) and was described by Feldman (71b) and Skinner (240). Schiller *et al* (221) presented a 67 year old man who complained of cold feet and legs, and numerous small, skin colored and hemorrhagic growths on the dorsum of the feet. There had been some degree of skin discoloration for about 10 years, and recently sharp pains had occurred in the area of discoloration.





36. Macular lesions.
37 Macular lesions.

B. Objective Symptoms

The initial manifestations may be a macule, nodule, plaque, an area of infiltration, or even purpura. The initial lesion usually appears as a reddened, well demarcated macule. The early macule progresses and becomes elevated, the color darkens and bluish red nodules or plaques appear Frequently both macules and nodules are present, but occasionally the eruption consists of one or the other alone, or one type may predominate.



38 Macular lesions
39 Nodular lesions.

1 Edema. This symptom was probably overlooked by Kaposi, since it is not mentioned in his otherwise exhaustive description of the disease. The explanation probably lies in the fact that his patients were examined when the disease was far advanced, at which time it is exceptional to find a case without multiple nodules and infiltrations Philippson (197) was the first to describe edema as a single manifestation.

Edema of the extremities is common in Kaposi's sarcoma. It may be the first manifestation of the disease and may precede any other lesions by months or years, as in Stats (240 case 1) patient, and those reported by Dalla Favera (52)

Mierzecki (169) and Hansson (108). In other instances swelling may occur late in the course of the disease. Several types of edema may occur. Stats states that it may take the form of pitting edema, in many ways superficially similar to the edema seen in other diseases such as congestive heart failure. It is



40. Plaque-like lesions.

usually symmetrical and is somewhat alleviated by elevation of the part. There is sometimes an unusual tendency to terminate sharply below the knee; the foot and leg being several times larger than normal in size while the knee and thigh are of normal proportions, as in two of his patients (248 cases 1 and 3). At other times the thigh is also involved in the process and a similar picture has also been observed

tumors do not appear until a relatively late stage. This edema, in association with Kaposi's sarcoma, was first described by Pick (198a) Hansson's patients, both women, had evidence of lymphangiectatic elephantiasis, and one patient had leg varicosities which had caused discomfort for twenty years. Little is known regarding the course of this type of disease and the diagnosis is often difficult. The following case (108) illustrates the difficulties encountered by both the clinician and pathologist. This patient, a 40 year old woman, had, 17 years previously suddenly developed marked edema of the leg, pelvis and right labium majora in the course of a few days. This edema did not subside and two years later was diagnosed as elephantiasis, plastic surgery was performed with no improvement. Nine years later several small cutaneous tumors appeared on the lower leg which were at first skin-colored and later became reddish-blue. This condition was diagnosed as sarcoma and amputation of the leg above the knee was performed. Histologic examination revealed vascular sarcoma, which the pathologist believed to be malignant, and also considerable edema of the tissues. Eight years later several pea sized, reddish blue cutaneous tumors appeared between the toes of the left foot. The histological diagnosis of these lesions was Kaposi's sarcoma. Treatment consisted of 15 mg. radium applied to the tumors for two hours. The lesions diminished and paled in color and at the final examination, 22 years after onset of the disease, she was found to be free of symptoms.

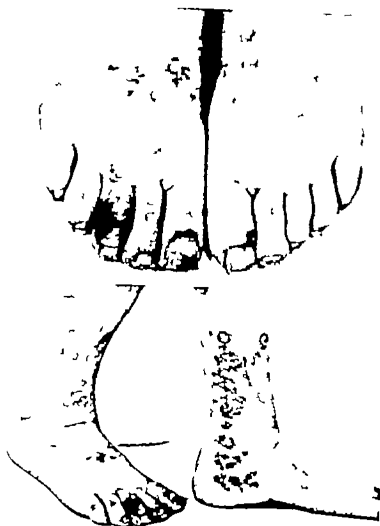
2. *Hemorrhage* Dilated blood vessels (telangiectasia) may at times, be visible in the nodules and plaques or in apparently normal skin, according to MacKee and Cipollaro (153b) Petechiae and purpura are occasionally present. The occurrence of localized and widespread purpura with the development of nodules and plaques has been reported by a number of observers, among them, Philippson (197) Mendes da Costa (165) Kaposi (132a) Dillard and Weidman (55) Havas (112) and Pelagatti (194)

Ravaut and Cachera (205) described a 65 year old man with Kaposi's sarcoma associated with arteritis of the lower extremities and a purpuric syndrome. The disease was of 18 months duration. Roentgen examination disclosed extensive calcification of the arteries of the legs. Although he had no extensive hemorrhages, numerous petechiae were present on the legs, the bleeding time was prolonged and the blood clot nonretractile.

Philippson (197) emphasized that hemorrhage, infiltration about the blood vessels, proliferation of the vessel wall elements and formation of new blood vessels were manifestations of the influence of a toxin which he believed was due to an unknown microorganism. His first patient had typical nodules of Kaposi's sarcoma for six months when a generalized, hemorrhagic, purpuric like eruption suddenly appeared. Some hemorrhagic spots receded entirely but others were replaced by new typical nodules. Approximately six months elapsed between the appearance of the hemorrhagic spots and the appearance of fully developed nodules in the same area. Three months later another hemorrhagic eruption, limited to the lower extremities, appeared, later still, another generalized eruption appeared. Each exacerbation of hemorrhagic lesions was followed by the development of some new nodules. The second patient had a similar eruption involving both legs and the left forearm which also gave rise to new nodules. These hemorrhages were an unfavorable sign, however since typical nodules soon appeared in these areas.

The 78 year old man described by Mendes da Costa (165) had extravasations of blood on both lower extremities followed by typical nodules of Kaposi's sarcoma in these areas. He concluded that extravasation of blood is the earliest sign of the disease.

Dillard and Weidman (55) favored the conception that hemorrhage was a primary factor in the production of these lesions. They believe that hemorrhage may be secondary to such factors as exposure to cold, arteriosclerosis, or ergotism, and, as the blood disintegrated the substance produced



43. Hemorrhages of the toe.
44 Hemorrhages of the toes and legs.

might, in some cases, be irritating to the endothelial cells and act as stimuli to their proliferation.

However Kaposi (132a) considered hemorrhages a relatively late symptom. It is possible that he observed this phenomenon without attaching a great deal of significance to it, since he mentioned the development of sarcomatous nodules in areas of preceding cutaneous hemorrhage in one case.

The presence of numerous small nodules within a large hemorrhage on the thigh was observed by Dalla Favera (52). Others who have described hemorrhages are: Havas (112), Funk (84), Koebner (137a), Bernhardt (19), Riehl (207), Pelagatti (194), Pick (198a), Mariani (160), Brann and



45. Lymph[illegible]gioma-like tumors. (Courtesy of Francesco Ronchese, M.D.)

Seuffer (28) and Semenow (231) Hemorrhages from the nose, mouth, intestinal tract and lungs, have also been described by Semenow (231) Paolini (189) and Brann and Seuffer (28) Changes analogous to those in the blood vessels are found less frequently in the lymphatic vessels (210c) Such observations were recorded by Pick (198a) who described large lymphatic cysts on the extremities which became slightly hemorrhagic and later developed into typical Kaposi nodules These lymphatic cysts did not always become hemorrhagic sometimes typical nodules developed directly from clear cysts.

A hemorrhagic tendency was described by MacKee and Cipollaro (155b) Dalla Favera (52) Andrews (6c) and Denzer and Leopold (54) The degree of edema is occasionally affected, to some extent, by local hemorrhage, according to Stats (246) This occurs in the form of large subcutaneous hematomas, purpura, or bleeding of a mucosal tumor Infrequently there may be a generalized purpuric state The histology of the Kaposi lesion explains some of these manifestations. Hemorrhage is the usual microscopic finding. It originates in the telangiectases and, since it occurs in close proximity to nodules or plaques, some cutaneous bleeding can be attributed to these lesions. In other cases, purpura appears on apparently normal skin. During this resorption of hematomas, clusters of Kaposi nodules may appear in an area of fading purpura, as mentioned by Dorffel (56) In the few cases in which studies have been made, no abnormalities of the bleeding or clotting mechanism which would account for these bizarre manifestations were found. Operative wounds do not bleed excessively in these patients and the mucous membrane bleeding is apparently always due to hemorrhage from a Kaposi nodule according to Stats. Excessive epistaxis or bleeding from the gums has not been noted. He (246 case 3) described a 43 year old woman whose illness began 11 years before with edema of both legs and a painless, colorless swelling near the right ankle Eight years later a similar but bluish swelling, appeared on the left ankle and numerous, painless,





48. Lymphangioma-like tumors. (Courtesy of Francesco Ronchese, M.D.)

4[illegible] Ulcerated lesions of Kaposi's sarcoma

bluish nodules then appeared on the lower extremities, accompanied by widespread spontaneous ecchymoses and progressive weakness.

3. *Nodules.* Kaposi (132a) described the classical lesions as nodules "ranging from the size of a pepper corn to that of a pea or a hazel nut, and brownish red or bluish red in color appear in the skin without apparent cause, either local or general. They are smooth on the surface, elastic in consistency and very often resemble blood blisters. They may occur singly or in plaque-like groups When in patches, the central portion of the induration is degenerated and gives rise to a discolored depression. The nodules generally develop first on the soles or the dorsum of the foot, thereafter spreading rapidly to the hands. Most of them appear on these parts. During the course of the disease, single or multiple tumors also appear although in lesser numbers, on the legs, arms, face and trunk. The nodules sometimes atrophy and may ulcerate at a later stage Finally similar tumors develop in the mucous membranes of the mouth and in the mucous membranes of the ventricles and the intestines.

The lesions may be discrete coalescent, and even conglomerate, according to MacKee and Cipollaro (155b) Occasionally they are closely crowded together forming large and small masses or tumors. They are firm, often shiny and rarely translucent. The nodules range from pin-head to bean size or larger and there may be only two or three lesions, or they may be numerous. The nodules, round or oval in shape are about 2 cms in diameter They are raised, flat, deeply pigmented, or of a brownish or purplish red color markedly indurated. The disease appears to extend deeply into the corium. Babes (8) described one patient who had 450 lesions.

The lesions usually occur in multiples, not infrequently in dozens, sometimes in hundreds, and rarely in ones or twos, according to Symmers (254a) Even in the earlier stages of evolution, the nodules are recognizable and when the disease is well developed there are reddish or purplish nodules, plaques and plateau-like formations. Usually the smaller

nodules are rounded, the plaques present a flat or nodulated surface, and the plateau like growths are irregular nodular and undulating. The individual nodules may vary from a few mms. to 2 or 3 cms. in diameter while the plaques and plateau-like growths may reach enormous proportions, varying from 5 to 20 cms. or more. The nodules do not appear to coalesce; the plaques and plateaus appear to represent the expansion of multiple large and small nodules, closely apposed to one another. Another remarkable clinical feature of Kaposi's sarcoma, according to Symmers, is the frequency with which certain of the smaller nodules lose their reddish or purplish appearance and become yellowish, faintly speckled by red or sometimes by light green. They disappear gradually without assistance, leaving smooth whitish or brownish scars, to be replaced in time by new nodules in the immediate vicinity or at a distance from the old. As the disease progresses, the collagenous tissues in the vicinity of these nodules become thickened, lymph stasis occurs and the skin is thrown into folds so that the extremity presents much the same appearance as that involved by the nonparasitic form of elephantiasis. Finally the growths may ulcerate, usually as a result of trauma, and sometimes produce superficial excoriations and, at other times, open lesions of formidable dimensions.

The patient presented by Ormsby and Mitchell (186a) had a *solid edema of the legs and feet*. Many nodules, varying from a pea to a small coin in size, were distributed over these areas. There were lesions on the buttocks and one on the glans penis. Wile (279) commented on the large number of small nodular lesions, which had not coalesced to form plaques and which he believed to be somewhat unusual.

In rare instances the disease may appear in the form of tumors from the onset (the "d emblee type) *as mentioned* by Buccellato (32)

4 Ulceration of Nodules. Although not frequent, ulceration of nodules may occur As a rule lesions on the upper extremities do not ulcerate while those on the lower extrem-



48 Ulcerated lesions of Kaposi's sarcoma.

ities ulcerate as a result of lymphedema and vascular obliteration.

Ulceration of the nodules was described by Hansson (108 case 4) in a patient with several small, bluish red, slightly painful tumors on the dorsal aspects of the hands and feet. These lesions extended, increased in size and a tumor of the left foot began to ulcerate. After roentgen ray therapy all

the tumors disappeared. However recurrence of the lesions *on the dorsum of the foot* necessitated amputation.

A 65 year old man who developed lesions on the backs of the hands ten years before, was presented by Wise (285c) Recently a group of dime-sized plaques, which underwent involution, had appeared on the palms. In the discussion of this case, Fox (80a) stated that ulceration was an unusual feature, since Kaposi's sarcoma is characterized by lack of ulceration, and the small size of the lesions. In his opinion, large tumors do not occur as in mycosis fungoides.

Bernstein's (20) patient had a boardlike, blackish brown infiltration of the right leg with ulcerations, pigmented nodules in the area, and many infiltrated pigmented spots on the entire trunk, with some infiltrations on other parts of the body The cutaneous changes had previously been regarded as varicose vein stasis dermatitis, and the ulcerations were ascribed to an injury Bunch (31) commented on a 30 year old man who developed lesions on the right foot, followed by *lesions on the internal malleolus, and later on the left foot* and ankle. The lesions were first brownish, then purple, and then became indurated. They became ulcerated and painful on the dorsum of the second and third toes of the left foot. A 56 year old man who developed a hard nodule on the back of the hand was reported by Ochs (183) Shortly after excision of this lesion, nodules appeared on the hands and feet, and one *lesion* on the back of the right hand became ulcerated. Two patients having ulceration of the tumors were reported by Ronchese and Kern (210b)

The patient presented by Meyers and Jacobson (167) was an 82 year old American who developed pruritus and burning along the medial surface of the right leg. One month later a small nodule appeared just below the knee, grew rapidly and was sometimes tender and painful This lesion later ulcerated and bled rather easily A patient who first developed lesions on the left foot and leg 20 years previously was reported by Dorffel (56 case 12) *Later lesions appeared on* the left arm and hand which were ulcerating and fungating.

Ulceration, in the early stages of Kaposi's sarcoma, may closely resemble stasis ulcers, according to Farber *et al.* (69) One of their patients required amputation of the leg, and the second patient obtained relief of pain and apparent resolution of the cutaneous lesions following roentgen ray therapy

5. Plaques and Infiltrations. The plaques are usually fairly well marginated and range in size from a dime, or smaller to an adult hand, or larger They may be round, oval or irregular in shape. At first there may be only slight infiltration, which becomes more pronounced as the lesions grow older Not infrequently a combination of infiltrating plaques and discrete nodules produce an extensive hard swelling of the



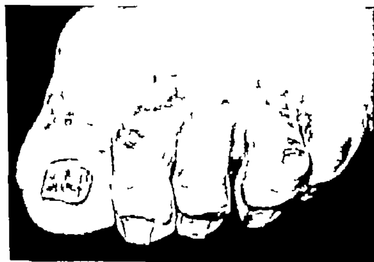
49 Plaques and infiltrations. (Courtesy of Francesco Ronchese *Postgrad Med*)

50 Cutaneous pigmentation of the feet and legs resembling Schamberg's disease

hands, feet, arms or legs, which may attain the proportions of elephantiasis.

The entire cutaneous surface may become involved, according to Funk (84) The skin of the extremities, buttocks, and abdomen, as well as the subcutaneous tissue, becomes diffusely infiltrated, of board like consistency and immovable, with an uneven surface which is nodular and of a dark violet brown (plum) color He found that nearly all patients had plate-like depressions in isolated nodules and in entire groups of nodules as a result of central resorption, while occasionally many nodules disappeared entirely

At times, the cutaneous lesions acquire a locally infiltrative character assuming the aspect of plaques, to produce a rough, board-like swelling of one or more extremities, and marked enlargement may result. Tissue augmentation ascribed to tumor infiltration was reported by MacKee and Cipollaro (155b) Aegerter and Peale (2) and Ormsby and Montgom



51 Cutaneous pigmentation of the toes resembling Schamberg's disease

ery (186b) There may also be blockage of lymph drainage, either by local infiltration in the lymphatics or regional obstruction at the trunk. Thickening of collagenous tissue areas adjacent to the skin nodules may further impede lymph drainage and accelerate the swelling Goldschlag (90) and Dillard and Weidman (55) commented on localized sclerodermic changes in the extremities and trunk as a cause of swelling, and a similar process was noted by Stats (248 case 3) There may also be more or less widespread, red blue infiltrations in the skin, according to Hansson (108) Like the tumors, they are often localized on the extremities, although in more advanced stages of the disease, they may also appear on the trunk, face and mucous membranes of the mouth. He found these infiltrations, as well as tumors, present in six of his patients. A 42 year old man, presented by Oppenheim (165) had symmetrical bluish spots and infiltrated plaques with a smooth surface involving both soles, the lateral aspects of both feet and over the ankles.

6 Unusual Manifestations.

Varicosities and Unusual Pigmentations Many bizarre features may be present in the early stages of Kaposi's sarcoma. Not infrequently the onset of the disease is manifested by a pigmentary disturbance resembling Schamberg's disease, and the presence of varicose veins, particularly in young adults.

Vascular changes may appear as varicosities with tumors distributed along the vessels and fixed to them, according to Dorffel (56) In 1899 Funk (81) first noted the presence of venous ectasia and coiled, enlarged veins near the tumors. The same year Kaposi (132c) presented a typical case with dilated veins of the lower extremities. Distribution of Kaposi sarcoma nodules along the venous system was also noted by Sellei (230) Philippson (197) Halle (105) Selhorst and Polano (229) Mariani (160) Dalla Favera (52) Ehrmann (61) Bruno and Scuffer (28) and by Hedge (114)

Two patients who developed scaling, pruritic patches around the ankles were described by Farber *et al* (69) Both had

mild venous insufficiency and, after several months, developed clinically and histopathologically recognizable Kaposi's sarcoma. These cases illustrate how Kaposi's sarcoma, in its early stages, may simulate stasis dermatitis and stasis ulceration of the legs.

Pigmentation extending to the plantar aspect of the foot and dorsum of the toes frequently develops. Stasis dermatitis seldom, if ever produces pigmentation in these areas. Palpation of the individual lesions in Kaposi's sarcoma reveals induration. Stasis dermatitis and ulceration may be associated with rather marked sclerosis of the skin in the affected area and around the ankles, but indurated nodules are not present.

Perrin (195b) states that, not infrequently the disease begins with purple discoloration in diffuse patches, very often symmetrical, on the hands and feet and begins more often on the flexor than on the extensor surfaces.

Burckhardt (33) reported a 43 year old man who had red, *painful and pruritic maculo-papular lesions on the soles of* the feet. A patient described by Skoblo (241) was a 74 year old man with septic thrombophlebitis of the right leg which resolved readily with administration of penicillin. There was an eruption, of at least two years duration, on the backs of both wrists, the feet and legs. The lesions, more or less symmetrical, were nodular and macular discrete, oval in shape, and varied between ½ to 2½ cms. in diameter their surface was smooth and shiny This case illustrates that well marked edema of the legs does not necessarily occur only in the more advanced stages of Kaposi's sarcoma. In the majority of cases it is an early symptom. In discussing this case, Lemberger (149) described a patient whose only symptoms were hematuria and bilateral, well marked edema. Three or four small bluish spots were later noted on both legs and, within two years time the condition developed to be Kaposi's sarcoma. He believed that edema is almost invariably present and is often a very prominent symptom of this disease

Patients having extensive thrombophlebitis have been reported by Lieberthal (151a, 151b) and others. On postmortem



52. Kaposi lesion simulating stasis eczema.
53. Macular hemorrhagic discoloration of the foot.

examination, Saphier (219) found enlarged and indurated venous stems and nerve trunks. Histologically along and within the vessel walls and sheaths of nerve trunks, there was tissue typical of Kaposi's sarcoma. Brann and Seuffer (28) observed the development of such a tumor from its origin from the wall of the vessel to its attachment to the skin within 24 hours.

The patient reported by Webster (274) displayed a prominent venous network on the palmar surfaces of the left hand and enlarged veins of the right forearm. He believed it un-

common to find small, localized areas of telangiectasia on the trunk, which later developed into typical Kaposi's sarcoma lesions. In addition to the typical cutaneous lesions this patient had deep-seated, bluish-green, branching streaks on the legs, which, in places, widened out in the manner of varicose veins and were firm and palpable through the skin. Histologically the smallest of these streaks were found to be cavernous vessels without accompanying changes. However those of a diameter larger than 2 to 3 mms. showed aggregations of spindle cells closely packed about many small blood spaces, with some pigment deposited in the region. When these regions were followed in serial sections, it was found that the blood spaces became confluent and terminated in a thin walled vein, without spindle cell mantle, at the point at which the streak narrowed. In the light of such facts, Webster believes that the venous network on the left hand was a prodromal manifestation, presaging the appearance there, at a later date of typical cutaneous lesions, had the patient lived.

Lack of Pigmentation. The patient described by Wolf (287) was a 48 year old man who had an eruption of nine years duration on the feet, legs, thighs, trunk and upper extremities. There was diffuse bluish-red infiltration on the outer and inner side of both feet, and several bluish nodular lesions on the back of the right knee. There were slight elevations which were firm on palpation on the trunk and upper extremities. These skin-colored lesions gradually developed into typical bluish-red nodules, according to Peck (193). Pollitzer (199b) commented that Kaposi's original name was idiopathic multiple pigmented sarcoma, but pigmentation was absent in this patient.

Pautrier and Diss (191b) described a patient whose lesions began as small colorless, painful, deep-seated nodules, detected only by palpation, which later assumed the characteristic violaceous hue.

Trophic Changes. The 40 year old man, presented by Costello (48a) had a cutaneous eruption of seven years duration which was accompanied by edema of the left lower extremity. He

also had leukonychia involving the distal two-thirds of the finger and toe nails. One of Symmers (254a case 8) patients had clubbing of the fingers

Verrucous Dillard and Weidman (55) and Pautrier and Diss (191b) called attention to lesions of a verrucous character In a discussion of Schiller *et al* (221) Finnerud (73b) stated that an almost constant finding, and one not usually noticed, is the warty character of the skin of the sides of the dorsum of the toes. Bloom (25b) in a discussion of Andrews (6b) called attention to the verrucous eruption on the dorsa of the toes, which may appear before any typical lesions of Kaposi's sarcoma.

Wise s (285d) patient had a raised globular verrucous lesion the size of a small pea, on the left cheek which had been present for three months and resembled a basal cell epithelioma There were arciform, raised, smooth, purplish infiltrated plaques and early superficial lesions on both palms and fingers. Similar various sized, infiltrated plaques, raised and superficial, were on the outer and inner borders of the sole of the left foot and on all the toes. There was a palm sized, superficial, infiltrated plaque on the outer surface of the right heel, with similar plaques on the inner aspects of the sole and on the first and second toes, and three isolated, pea sized, purplish lesions on the anterior aspects of the left leg. The left foot and ankle were edematous Small lymph nodes were palpable in the anterior cervical and axillary regions.

Bullous Other unusual cutaneous features consist of glistening, somewhat translucent nodules which resemble thick-walled vesicles, bullae and lymphatic cysts such as are seen in lymphangioma circumscriptum, according to MacKee and Cipollaro (155b) These are the size of a pea or a cherry and may be pinkish, brownish or bluish in color Such lesions have been described by Pick (198b) Ormsby (166b) Frost (83) Dillard and Weidman (55) and Wise and Eller (285e)

Klaber s (135b) patient had extensive sheets of deep lilac colored edematous infiltration, which was fairly depressed, on both hands and feet. On the forearms and legs were

numerous discrete round or oval lesions, of similar character On both ankles there were markedly edematous areas which were almost bullous in character A few nodules had appeared on the right buttock within the past few months.

A patient with edema and bullous lesions on the legs was presented by Rothman and Henningsen (213) It is also noted that in Kaposi's sarcoma, especially on the lower extremities, there are occasionally soft, reddish brown nodules which can be pushed into the skin, well below its level, and which gradually reappear in the course of a few seconds, to resume their puffy appearance. This soft, almost cystic consistency of the lesions is probably due to lymph stasis. This feature was also noted by Ronchese and Kern (210c) in two patients. A 72 year old Italian woman who had a bleeding tumor of the left index finger was reported by Turrey (253) Both hands were diffusely cyanotic, with patches of deep purple color On the sides of the fingers, were regularly shaped areas of infiltration some flat, others pea sized. Another pea sized area of infiltration involved the right great toe and there were purplish red, flat, blotch-like infiltrations on the middle of the sole. Histologically the finger lesion confirmed the diagnosis of Kaposi's sarcoma. In the discussion, Morrow (173) called attention to the large vesicles in the webs of the fingers. He believed these symptoms to be rare in Kaposi's sarcoma, although they were characteristically present in this patient.

Wise and Eller (255e) described bullous lesions in a 66 year old woman who developed reddish brown, violaceous patches on the neck, hands and feet, 15 years previously These lesions increased slowly in size and in the depth of color Four or five years after onset the disease was nearly generalized, including the face and, to a lesser extent, the scalp. On the anterior and posterior surfaces of the right thigh, there were large areas of closely grouped vesicles and bullae, both isolated and fused. These vesiculobullous lesions arose in infiltrated and thickened areas of skin. The bullae ruptured easily and spontaneously emitting a profuse nonfetid, clear watery discharge which caused the affected area to be moist



54 Verrucous lesion of the toe.
55 Development of spindle cell sarcoma in lesions of Kaposi's sarcoma.

and uncomfortable. While the lesions were not typical of true vesicles and bullae, they were analogous to the vesicular efflorescences of lymphangioma circumscriptum, so far as the fluid content was concerned. They arose as a result of lymph stasis caused by constricting bands of skin above the ankles which gave rise to an intense lymphedema of the skin above the constricted area. This edema eventually caused the formation of the vesiculobullous lesions. Histological examination revealed a characteristic angiomatous sarcoma, the tissues exhibiting an unusual degree of lymphedema. These lymph cysts in Kaposi's sarcoma have also been described by Dalla Favera (52) and Pick (198a).

On the other hand, Trimble (261) stated that bullae do not occur in Kaposi's sarcoma. The lesions are lymph vesicles, rather than bullae, which are formed in connection with the lymph stasis. Akwa, *et al.* (4) described a 53 year old Greek man who developed a bean sized vesicle which contained dark fluid. One week later the ball of the foot became painful and bluish discoloration appeared on the dorsum of the foot. Eleven years later the histologic diagnosis of Kaposi's sarcoma was made. Six years later bluish papules appeared on the lower part of the left leg as well as on the hands.

Rostenberg (212) presented a 56 year old man who had developed lesions four years previously. On the sole of the left foot there were a number of isolated reddish to bluish macules, from 3 to 6 cms. in diameter which appeared to be walls of the bullae on pressure. One of them contained a clear fluid. There was a band like area underneath all the toes, about 8 cms. wide, which had the same reddish appearance as the smaller lesions and also appeared to be the wall of a large continuous bulla. On the dorsal surface there was one prominent lesion the size of a large pea, on the second toe, which on pressure also appeared to be bullous. The first and second toes were considerably enlarged and the bony structures were also involved.

A 39 year old man, reported by Gougerot, *et al.* (92c) had polymorphism of the lesions associated with bullae general-

ized arthralgia and erythematous stomatitis He had developed successive and continuous crops of purpuric papules on all four extremities during the preceding four months. These lesions developed in two or three days time then disappeared or became necrotic and encrusted. There were also several bullae on the thighs and large thickened red plaques on the backs of both wrists.

7 *Evolution of Eruption.* As a rule, the eruption evolves slowly and the affection is progressive according to MacKee and Cipollaro (155b) Old lesions often undergo spontaneous involution, leaving atrophy depressed scars and pigmentation. At the same time, new nodules or plaques appear Occasionally grouping of lesions, and especially the development of nodules at the periphery of older lesions, produce a configuration suggestive of syphilis. The tumors grow slowly and after a variable period of time spread over the skin and involve the viscera, particularly the lungs and the lymph nodes. Hemorrhages from the cutaneous lesions and viscera frequently occur and there may be edema of the leg or the foot, and elephantiasis-like changes The rate of progression is slow and variable spontaneous remission and regression of the lesions sometimes occurs, leaving pigmented atrophic scars. The duration of life averages between five and 10 years death being due to intercurrent infection, cachexia, visceral involvement or repeated hemorrhages.

Andrews (6b) reported a 50 year old man who developed a purple plaque on the medial side of his left ankle seven years before. During the last three years purple plaques and nodules, varying from dime to silver dollar size developed on each leg, and similar indurated plaques appeared on the right ankle The toes assumed a frostbitten appearance which had persisted. During the past two or three years the trunk had become involved, and in the past year the upper extremities and the face

There are frequently variations in the classical macule nodule and plaque formation, according to McCarthy and Pack (153) One type evokes marked fibrous reaction and clinically

resembles neurofibroma. In one of their cases the disease was rather indolent and remained localized on the leg for 10 years. Old lesions will often regress into a flat pigmented scar in the periphery of which new nodules may develop. Still another type is composed of pink translucent nodules similar to lymphangioma. Lymphadenopathy is common in all phases of the disease, and the nodes may or may not contain actual spindle cells. Ultimately the tumors may appear in the submucosa of the entire gastrointestinal tract and lungs as friable, hemorrhagic, polypoid masses. This development marks the transition into a terminal phase when death from exsanguination is imminent. Not uncommonly the tonsils, thoracic and abdominal nodes and bone are invaded by the tumor. Three of their patients (153) had involvement of the oral cavity, four had involvement of the lungs, two had bone involvement and one had involvement of the liver and spleen.

Deviations from the typical cutaneous onset have been reported and the tumors may originate in practically any part of the body. However prior to Dorffel's (56) monograph in 1932, it was generally believed that all extracutaneous lesions were metastatic, inasmuch as up to that time few cases had been described in which cutaneous lesions were absent or had been preceded by visceral lesions. Since then several patients having tumors in the viscera, not associated with cutaneous manifestations, have been described. Primary Kaposi's sarcoma in the heart was described by Aegerter and Peale (2) and Chosser and Ranney (40), in the kidneys, liver and intestines by Tedeschi, *et al* (257), in the lymph nodes and mucous membrane of the penis by Barringer and Dean (13) and in the eyelid by Graham (93). This evidence suggests that Kaposi's sarcoma may be a systemic disease of multicentric origin and long duration with little tendency to metastasize. Sequeira and Brain (233d) believed that in these cases the growth appears to undergo retrogressive changes with formation of depigmented depressions.

The development of true spindle cell sarcoma in a patient with Kaposi's sarcoma was reported by Sequeira and Brain

(233d) This man developed a purplish discoloration of the skin just above the left ankle at the age of 44 years. The condition spread slowly and after six months time completely covered the dorsal surface of the left foot. The following year lesions appeared on the right foot and slowly increased in size a year later similar lesions appeared on the dorsum of the left hand and wrist. These latter lesions were pruritic and the feet became painful and edematous. The dorsal surface of the left foot was red and swollen, with an area of raised purple infiltration across the instep the lower limit of which was an almost straight line between the malleoli. On the inner side, this line was made up of small discrete papules The toes were almost immobilized by a sclerodermatous condition of the skin covering them. About 5 cms. above the internal malleolus was a discrete, roughly square-shaped lesion, 1.5 cms across, consisting of a raised, purple flat topped nodule. On examination 13 years later the skin of both feet, and extending 2 inches above the ankles, was hard and thickened, and produced some limitation of motion There were numerous, scattered, purplish-red, soft, slightly raised nodules of varying sizes over the upper part of the legs A fungating mass, arising from one of the outlying vascularized nodules, then appeared on the front of the shin and the leg was amputated.

The patient described by Forman (79c) developed an ulceration involving the inner aspect of the left ankle and foot 28 years after the onset of Kaposi's sarcoma. Histopathological examination disclosed a probable prickle cell epithelioma. Gross (101b) reported an 81 year old man who presented several bluish red, somewhat infiltrated patches of firm consistency on both ankles The surface of these lesions was slightly scaly and hypertrophic. There was moderate edema of both feet and slight verrucous hyperkeratosis on the dorsal surface of the toes. There was a round, dark red lobulated tumor with a narrow base the size of a large marble on the outer aspect of the left foot. The surface was partly denuded and covered with a greyish bloody exudate The histological

examination of the fungating tumor showed changes of low grade spindle cell sarcoma. Satenstein (220b) stated that many cases of Kaposi's sarcoma frequently have fungating tumors. This was a comparatively common finding, when injury to a tumor occurred and destroyed the skin covering, causing the tumor to grow outward rather than inward, thus resulting in a fungating lesion.

C. Hemogram

In the majority of cases the hemogram is normal. Anemia is present in many cases, according Dorffel (56) who reported one patient with a hemoglobin of 33 per cent, others with varying degrees of anemia and some with normal hemoglobin values. Similarly the red blood cells numbered from two and one-half million per cu. mm. to normal. MacKee and Cipollaro (155b) state that secondary anemia is quite frequent and may be severe. The skin color of patients having marked anemia was described as clay or lemon colored by Bernhardt (19), De Amicis (53), Riehl (207), and others. The occurrence of anemia has also been reported by Steiner (247), Hartzell (111), Funk (84), Mariani (160), Lieberthal (151a) and Dillard and Weidman (55).

There is no characteristic total white blood cell count, as revealed in a study of cases in the literature by Dorffel (56), although a few patients had definite leukocytosis. There were few abnormalities in the differential white blood cell count. There was occasional disturbance in the relative proportions of polymorphonuclears and lymphocytes, but these were usually not significant. The most striking feature was the considerable degree of monocytosis. Two patients with an increase of reticuloendothelial cells and monocytes was reported by Bertaccini (21c). In these cases, and in two others, he found concomitant deviations from the normal hemogram of the peripheral blood, mainly a marked monocytosis. Flarer (77) described 60 per cent abnormal monocytes in the peripheral blood, with a marked shift toward cells of the lympho-mono-

cytic series. Wende (276) reported 12.12 per cent large monocytes, Dalla Favera (52) 28.2 per cent large monocytes and 9.9 per cent transitional cells, Grigorjew (98) 22.5 per cent transitional cells and 6 per cent eosinophils, Rottman (214) 5.5 per cent monocytes, Winternitz (282) 8 per cent monocytes and 9 per cent eosinophils, Paolini (189) 8 per cent monocytes, 3 per cent eosinophils, 2 per cent Turck's cells, Bechet (14) 9 per cent monocytes, 8 per cent eosinophils, 1 per cent transitional cells, and Vigne (266a) 9 per cent monocytes and 5.5 per cent eosinophils.

Dorffel (58) found eosinophilia to be less frequent than monocytosis. Hurlbut and Lincoln (124) also found that eosinophilia is not a constant finding, although 4 or 5 per cent eosinophils in a normal total leukocyte count was not uncommon, and occasionally counts up to 17 per cent were recorded. They did not observe monocytosis. Ellis (64) reported 46 per cent lymphocytes and Kusnezow (112) 55 per cent lymphocytes in the peripheral blood

Dupont (58b) reviewed the blood count changes in Kaposi's sarcoma, in which the peripheral blood was compatible with a leukemic syndrome and described three additional cases. Uncommon types of cells were found, which were classified according to two groups 1) an uncommon type of lymphocyte, and 2) more or less atypical large mononuclears. The first type has a kidney shaped, bilobate nucleus, either double or having one or two small bud shaped expansions

Changes in the sternal bone marrow comparable to those present in the spleen were occasionally observed by Tedeschi *et al* (257) Active hyperplastic bone marrow was found in two cases by Stats (246) although there was no change in the peripheral blood picture The changes were due in part to radiotherapy of the skin or splenic lesions He believes alterations in the hemogram are rarely marked and never of specific nature

Hemolytic anemia has been reported in association with Kaposi's sarcoma. This type of anemia is a fairly common finding in the lymphomas. The case described by Greppi and

Bettoni (97) is unique in that this patient had a microspherocytic hemolytic anemia with an enormous excretion of fecal urobilinogen. In addition there was marked granulocytopenia and the patient died with oral sepsis. The case of Unseglio, *et al* (264) may have been similar A moderately severe anemia and leukopenia were temporarily ameliorated by splenectomy but there was no definite evidence of a hemolytic process. Two of Stats (246 cases 1 and 2) patients had an active or hyperplastic sternal bone marrow with a normal differential count. Bertaccini (21c) examined the bone marrow of three patients with Kaposi's sarcoma, all of whom had a considerable monocytosis in the peripheral blood. Two patients showed an increase in reticuloendothelial and monocytic cells in the marrow Impression smears from Kaposi's tumor nodules revealed monocytoid cells similar to those found in the blood in certain cases of subacute bacterial endocarditis.

Martensson and Henrickson (161) described the clinical course and pathological findings of immuno-hemolytic anemia in a 63 year old man. He first developed what appeared to be idiopathic anemia, but one year later Kaposi's sarcoma was diagnosed at autopsy when angiosarcomatous changes were found in the lymph nodes, stomach, entire intestinal tract and very small lesions in one lung. There were no cutaneous manifestations. Splenectomy had no effect on the hemolytic process which did respond favorably to treatment with steroids. These compounds did not, however inhibit the growth of the lymph nodes although they regressed readily with roentgen ray irradiation, and a quiescent stage resulted, but soon other changes occurred. They believe that anemia of immuno-hemolytic type may occur in Kaposi's sarcoma as in other diseases of the reticuloendothelial system, and this case shows that hemolytic anemia may appear at a very early stage of the disease with minor pathologic changes. They believe this to be the third case of hemolytic anemia in association with Kaposi's sarcoma to be reported. The first case was described by Greppi and Bettoni (97) in a patient who had superficial changes of the

genitalia. The other patient, reported by Hogeman (120) was a middle aged man who had typical Kaposi's sarcoma of the skin, lymph nodes and internal organs in addition to a severe hemolytic anemia. The white blood cell and thrombocyte counts were also low The leukocytosis and thrombocytopenia were controlled by splenectomy but the hemolysis persisted.

The significance of these various splenic, hemic and bone marrow deviations cannot be assessed, according to Stats (246) There is a variability of findings. Some reports support the theory of marked reticuloendothelial system involvement. He believes the changes may be interpreted either as a reaction of this tissue to the presence of the tumor or a direct implication of this tissue in the process of neoplasia. Dorffel (58) has concisely presented some of the evidence in support of this thesis.

D Internal Organ Involvement

Although the skin is the primary organ involved in Kaposi's sarcoma, and many cases show no spread beyond the cutaneous site at autopsy it is not uncommon to find sarcomatous deposits in the viscera. Involvement of nearly every organ of the body has been recorded. Of more than 600 cases described from 1872 to 1949 Mitchell and Feder (172) found the common sites of involvement, excluding the skin, to be the penis, gastrointestinal tract, upper and lower respiratory tracts, and the superficial and deep lymph nodes. The uncommon sites were described as the serous membranes, spleen, liver adrenal glands, myocardium, mesentery diaphragm urinary bladder thyroid and brain.

In his series Dorffel (58) found the skin to be most frequently involved and the next most frequent site of involvement was the gastrointestinal tract from the mouth to the rectum. Next in frequency were the liver lungs, retroperitoneal and mesenteric lymph nodes. Less frequently involved were the spleen, pancreas, kidneys, suprarenal glands, peritoneum (including the omentum) testes, epididymis, trachea,

bronchi, pleura and heart muscles. Organs rarely involved were the central nervous system and the peripheral nerves.

Choisser and Ramsey (40) listed the involvement of visceral lesions, recorded prior to 1932, as occurring most frequently in all portions of the gastrointestinal tract, liver lungs, lymph nodes (retroperitoneal and mesenteric) frequently in the epididymis, trachea, bronchi, spleen, pancreas, kidneys, peritoneum, testes, and rarely in the nervous system, peripheral nerves, tongue, bladder muscles and pituitary gland. They listed the brain, thyroid, ovary and uterus as never having been involved. However cases of brain and thyroid involvement have been described by Nesbitt, *et al.* (176) and Schirren and Burkhardt (224)

Kaposi's sarcoma not associated with cutaneous lesions was first described by Dorffel (56) A patient described by Greppi and Bettoni (97) developed the primary lesion on the glans penis, the inguinal lymph nodes became involved and, at autopsy there was extension into the psoas muscle and nodules were found in the lung. Pearce and Valker's (193) patient developed a nodule on his gum several months before the skin became involved. Two patients with primary lesions on the glans penis were noted by Barringer and Dean (13) Cases in which the inguinal lymph nodes were the primary site of the disease were reported by Van Cleve and Hellwig (263) and Goldschlag (90) In the latter case, the original lymph node involvement was diagnosed as lymphogranuloma inguinale but he believed it to be an ungewohnlichem vorstadium of Kaposi's sarcoma In a case described by Statz (248) about 14 months intervened between the onset of the illness, characterized by symmetric edema of both lower extremities, and the appearance of circumscribed nodules on both legs.

It has been known for many years that the viscera and lymph nodes may become involved by a similar sarcomatous process, as mentioned by Dorffel (56) Choisser and Ramsey (40) Mackee and Cipollaro (155b) Dalla Favera (52) and Kren (139) Because of this, the disease is of general sig

nificance and must be considered in the differential diagnosis of a large group of systemic complaints and physical findings. In the first cases of this type observed, the visceral involvement followed the appearance of the cutaneous disease. More recently Stats (246), Mackee and Cipollaro (155b), Aegerter and Peale (2), Bilancioni (22) and Usseglio, *et al* (264) have noted that involvement of the internal organs may precede the appearance of Kaposi's sarcoma of the skin, and some, as Aegerter and Peale maintain that the cutaneous lesions may be lacking altogether. However, Stats points out, many cases of Kaposi's sarcoma of the skin progress slowly for many years and have been examined at autopsy without any indication of spread beyond the dermal apparatus. Many observers now believe that such foci are primary, that there is no metastasis. While the first manifestations of the affection are ordinarily in the skin, *there is evidence that other parts become involved* early, or simultaneously, and even that the disease may begin in the viscera.

The patient reported by Cholsser and Ramsey (40) had no cutaneous involvement and the lesions were primary in the auricle of the heart. This patient, a 26 year old man, was acutely ill. There was dyspnea, moderate cyanosis, and the great vessels of the neck were distended. The heart was markedly enlarged but there was no evident pulsation in the precordial or great vessel areas. Sounds were distant and without murmurs. The symptoms became rapidly more severe and he died six days later. The anatomical diagnosis was hemorrhagic neoplasm of the heart, with secondary nodules in the pericardium, mediastinum, pleura and liver, right hemothorax, hemorrhagic infarcts of the kidneys and advanced passive congestion of the liver.

Incidental involvement of the heart and pericardial sac, generally without clinical symptoms, is frequently recorded among the visceral localizations, and is described by Symmers (254a), Dillard and Weidman (65) and Stats (246). A primary and unique cardiac localization is more unusual. Almost simultaneously, in two independent papers, Weller (275) and

Choisser and Ramsey (40) described two cases of primary Kaposi's sarcoma of the right atrium of the heart, classified as angioreticuloendothelioma from the morphologic standpoint. However Stats suspects these two reports to be the same patient. Similar cases have been described by Culma Motta (50) and Aegerter and Peale (2) have added another case in which the only apparent localization of the disease was in the *right atrium of the heart. The identification of these cases as* instances of Kaposi's sarcoma was based on the close resemblance of the cardiac findings to those usually seen in association with the cutaneous manifestations of Kaposi's sarcoma. Whether or not the cases deserve to be considered as such is a pertinent point.

Paolini's (189) patient complained of intestinal symptoms *before the appearance of cutaneous lesions. At death, the* usual cutaneous manifestations and nodules of Kaposi's sarcoma were found in the large and small intestines and other viscera. Involvement of organs such as the intestines, lungs and bladder may be indicated by hemorrhage, cough, diarrhea, etc but definite clinical indications of involvement of other organs are likely to be absent, ignored or misinterpreted.

There is often no certainty of visceral participation until necropsy Philippson (197) Dalla Favera (52) and Hansson (108) described the finding of multiple cutaneous lesions without visceral involvement at autopsy There were no traces of visceral metastasis in Hansson's patient, despite the fact that the disease had been present for five years.

Occasionally an ante mortem diagnosis of visceral involvement prior to the appearance of cutaneous lesions is made. The same changes occur in the viscera as in the skin. This fact, together with simultaneous involvement of the skin and viscera, point to internal lesions as being of primary and independent origin, and not true metastasis, according to Becker and Thatcher (15b) True metastasis does occur after malignant degeneration, but *many case reports are indefinite on* this point

1 Lymph Nodes. A more or less generalized lymphadenopathy of limited extent or indefinite character may affect both the superficial and deep lymph nodes before the appearance of cutaneous lesions. This lymphadenopathy might easily be overlooked or misinterpreted, according to Tedeschi, *et al* (257) However lymphadenopathy does not necessarily indicate that the lymph nodes are involved in the process. They believe that it is difficult, at present, to discuss the significance of these changes One possibility is that they may represent a non specific inflammatory reaction, the other that they may represent early stages of development of the disease process.

Hyperplasia of the reticulum cells was believed by Dorffel (56) to account for this condition. He states that Kaposi's original conception was that the lymph node involvement occurred only when the sarcomatous lesions were ulcerated or secondarily infected. Subsequent observers held this same opinion. He described early involvement of the lymph nodes as characterized by swelling and proliferation of endothelial cells in the blood vessels and in the supporting reticuloendothelial tissues of the nodes.

In some cases there was no histological evidence of tumor tissue Dalla Favera (52) was the first to call attention to the fact that the enlarged nodes may not show typical focal changes. In his case the only detectable change was thickening of the fibrous connective tissue stroma of the lymph nodes. Greppi and Bettoni (97) described round cell hyperplasia and Goldschlag (90) found a chronic nonspecific inflammatory process. There was a sarcoid like picture in the case described by Wise (255d) The cases reported by MacKee and Cipollaro (155b) showed plasma cell infiltration, histiocytic phagocytes containing iron pigment, and a moderate thickening of the stroma of the lymph nodes. Cases without histological evidence of tumor tissue were also described by Stats (246 case 1) and by Dillard and Weidman (55) Frequently the lymph nodes are palpable and the swelling may be due entirely to inflammation, as described by Hartzell (111) and Stratton (252) At times, the early lesions are swollen and

there is proliferation of the endothelial cells in the blood vessels and supporting reticuloendothelial system of the nodes and several cases in which the lymph node histology was typical of Kaposi's sarcoma have been described.

Among those describing these features were Hartzell (111) Krupnikow (140) Mariani (160) Sellei (230) Stratton (252) and Wise (285b) Although it is not possible, at present, to assess these findings, they may represent the early stages of lymph node alteration before the tumor appears or may represent secondary inflammatory change, according to Stats (246)

On the other hand, Barringer and Dean (13) are of the opinion that the lymphatic nodes are not involved in this disease.

Stats (246 case 4) observed that, in early lymph node involvement, the tumor appeared first in the perivascular areas within the nodes. Often, such nodes were entirely surrounded by Kaposi tumor which did not invade the capsule. Lymph node involvement is frequently so marked as to be out of all proportion to other visceral involvement by tumor This may be construed as evidence favoring the general systemic nature of Kaposi's sarcoma and in this regard relates the disease with "lymphoblastomas or reticuloendotheliosis, he believes. The deep lymph nodes are more often enlarged than the superficial ones a situation which makes clinical detection difficult. The mesenteric and retroperitoneal nodes are usually involved although all or any groups of nodes may be affected. The lymph node involvement is not necessarily regional to an organ involved with Kaposi's tumor and, therefore, this involvement should not be regarded as a metastatic process. Enlargement of deep nodes can occasionally be ascertained clinically by palpation of irregular masses in the abdomen or by roentgenologic or clinical evidence of mediastinal or bronchial lymphadenopathy Histologically the appearance of the involved lymph nodes may be identical with the cutaneous tumors according to Stats.

Marked enlargement and matting of the hypogastric, paraor

tic, tracheobronchial, paratracheal, mediastinal and mesenteric lymph nodes were noted by Stats (246 case 2) On section, the nodes were fleshy or hard and grey to bluish brown in color and, histologically were partially or completely replaced by angiosarcomatous tissue. The cervical lymph nodes enlarged progressively in another patient (case 3) and at the time of death there was the aspect of a "bull neck. Another patient (244 case 4) had marked enlargement of the tracheobronchial, paratracheal and paraortic lymph nodes which were matted and adherent to adjacent structures. There was extension of tumor tissue into and around the suprarenal glands (the left was largely replaced by tumor) pancreas and kidneys, while the same process could be traced down the iliac vessels. The mesenteric lymph nodes were enlarged, fleshy and hemorrhagic, but not fused The involvement was most severe toward the root of the mesentery

Inguinal lymph node involvement was reported by Goldschlag (90) left submaxillary lymph node involvement by Arnaux, *et al* (7) and by Greppi and Bettoni (96) There was lymph node involvement in one case described by Mierzecki (169) and involvement of the mesenteric, cervical and gastro-hepatic lymph nodes in the case described by Dillard and Weidman (55) In Symmers (254a case 8) case there were palpable nodes in the left axilla, both groins and both popliteal spaces Becbet's (14) patient showed marked inguinal, cervical and axillary lymphadenopathy

2. Gastrointestinal Tract Involvement The gastrointestinal tract is second to the skin as the most frequent visceral localization All portions of the tract, from the mouth to the anus, may be involved The oral area, stomach and small intestines are most often affected the large intestine and appendix less frequently The oral manifestations are described under ETIOLOGY (Sites of Predilection)

The gastrointestinal symptoms are usually not prominent but patients having diarrhea, hemorrhage and hemorrhagic effusion into a serous sac have been described. Aegerter and Peale (2) reported severe diarrhea, abdominal pain and

hemorrhage and Paolini's (169) patient had severe diarrhea and abdominal pain. Stats (246) states that literally hundreds of nodules may be scattered throughout all segments of the gastrointestinal tract.

Pharynx. Bilancioni (22) described a 62 year old man whose voice had recently become gutteral and nasal, he had difficulty in swallowing and a sensation of obstruction in the throat. There was a mobile, rounded tumor in the hypopharynx but no lymphadenopathy He also had numerous tumors, some ulcerated, on the hands and feet. The histological diagnosis was Kaposi's sarcoma. Tracheotomy was performed and the hypopharyngeal growth removed. This lesion was found to have the same histologic structure as the cutaneous lesions. Involvement of the pharynx was also reported by Schirmunskaja and Tschotschia (223) and by Symmers (254a) A patient with lesions in the pharynx, described by Aranz, *et al.* (7) had a tracheotomy and the buccopharyngeal lesions were treated by electrocoagulation.

Stomach and Intestines. In the presence of gastrointestinal involvement, *the small intestine is more frequently involved* than the stomach. Stats (246 case 4) described a patient who had, throughout the gastrointestinal tract, in the greater curvature and fundus of the stomach, duodenum, jejunum, ileum, appendix, and colon, purplish, circumscribed, submucosal nodules, up to 1.5 cms. in diameter projecting from both the mucosal and serosal surfaces. At the point where the esophagus passed through the diaphragm, there was a condensation of tumor tissue which infiltrated the wall to the mucosal surface In another patient (246 case 2) there was a flat nodule 3 mms. in diameter in the submucosa of the greater curvature of the stomach. A few similar nodules were present in the mesentery and in the small intestine at the attached border Shining through the serosa of the free portion of the small intestines and the large intestines were many pea sized tumor nodules. These were all situated in the mucosa and submucosa and *were covered with intact epithelium.*

In Kusnezow's (142) patient the stomach was dilated and



56 Histologic section of tongue showing edema of subepithelial connective tissue and diffuse proliferation of capillaries. (Courtesy of Samuel J. Zakon, M.D.)

57 Involvement of ileum and jejunum. (Courtesy of Samuel J. Zakon, M.D.)

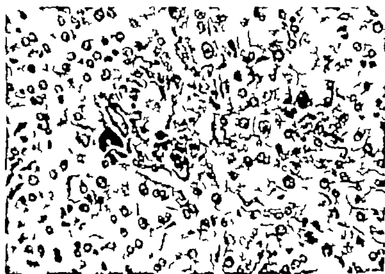
on the mucous membrane along the greater curvature, were many groups of dark blue, superficial, confluent nodules. There were two similar nodules in the duodenal mucous membrane. One nodule in the large intestine was located at the place of attachment of the mesentery and the others nearby.

Zakon's (289b) patient had lesions on the vermilion borders of the lower lip and tongue. He (289c) reported the autopsy findings three months later. The entire gastrointestinal tract, excepting the colon, was found to be studded with lesions of Kaposi's sarcoma. In spite of the fact that almost the entire lumen was occluded, the patient had never complained of gastrointestinal symptoms.

Barium studies of the gastrointestinal tract of Seagrave's (228) patient revealed numerous intraluminal masses of varying sizes, closely clustered together in the small intestine. There was evidence of low grade obstruction. Surgical examination revealed the entire small intestine to be involved. Pathological examination of 14 feet of the resected small intestine, showed large, blackish red, polypoid masses, ranging from 0.5 to 6.0 cms. in diameter projecting into the lumen of the bowel. There were 44 gross lesions counted in this specimen, 23 of which were concentrated within 18 inches of bowel. The lesions were irregular, moderately soft, had a fungating appearance and some were undergoing involution. In addition to the polypoid masses, there were numerous purple red nodules lying completely beneath intact mucosa and ranging up to one cm. in diameter.

A 17 year old boy who died of intussusception caused by a solitary Kaposi nodule in the ileum, was recorded by Tedeschi, *et al* (257). Involvement of the gastrointestinal tract was described by Aegerter and Peale (2, case 3) who state that the most common cause of death in Kaposi's sarcoma is involvement of the intestinal mucosa with ulceration causing hemorrhage and exsanguination. A 69 year old man who had involvement of the jejunum with perforation and peritonitis, was reported by Mitchell and Feder (172). He had cutaneous involvement for many years prior to the perforation of the





58. Mucosa of ileum replaced by a diffuse circumscribed infiltration. (Courtesy of Samuel J. Zakon, M.D.)
59. Involvement of the liver. (Courtesy of Samuel J. Zakon, M.D.)

secondary mass in the jejunum. They believe this to be the first report of perforation as a complication followed by peritonitis and death in Kaposi's sarcoma. Involvement of the gastrointestinal tract has also been described by Cholmer and Ramsey (40) and Weller (273) Dorffel (56 case 13) Van Cleve and Hellwig (265) and by Dillard and Weidman (55)

Liver Involvement of the liver has been reported by Van Cleve and Hellwig (265) Dorffel (56 case 13) and by Aegerter and Peale (2 case 3)

3. *Respiratory Tract.* Nearly all portions of the respiratory tract, with the exception of the nasal cavity have been involved by tumor nodules of Kaposi's sarcoma.

In one of Stats (248 case 4) patients, the pleural surfaces of the lungs were studded with irregular flat, hemorrhagic plaques which penetrated the pulmonary parenchyma in some places. There were several discrete tumor nodules in the right upper and left lower lobes. At the hilus of each lung there was a marked condensation and increase in firm, hemorrhagic tissue which invaded both lower lobes. The connective tissue of the mediastinum and retroperitoneal areas was largely replaced by hemorrhagic tumor tissue which bound the various structures to one another Tumor involvement, as extensive as in this case, had not been previously recorded and despite these widespread lesions, Stats states that symptoms related to such tumors are not common. In almost all instances the nodules remained small, well circumscribed and did not ulcerate

A patient reported by Becker and Thatcher (15b) presented angiomatous plaques in the parietal pleura, consisting of blood-filled spaces, lined and bordered in places, by elongated spindle cells. Involvement of the pulmonary parenchyma and pleura were described by Dalla Favera (52) Lung involvement was also described by Dorffel (56 case 13) and Greppi and Bettoni (97) Lesions of the lungs were found at autopsy in Mierzecki's (169) patient Dalla Favera (52) also described lesions in the bronchi A 45 year old man who had a lesion at the anterior end of the right ventricle of the larynx

was presented by Rothman and Henningsen (213). Involvement of the larynx was also described by Symmers (254a), Bilancioni (22) and Schirmunskaja and Tschotschia (223).

The patient reported by Kusnezow (142) had groups of bluish nodules on the mucous membrane of the trachea, particularly on the anterior surface, which were confluent and protruded into the air passage. Dalla Favera (52) also described involvement of the trachea.

Comel (45) described two men, aged 66 and 74 years, respectively who had lesions of Kaposi's sarcoma for several years. Both patients complained of cough and hoarseness and both had small nodules in the larynx and trachea which had the same histologic structure as the cutaneous nodules.

4. Spleen Involvement. Pathological alterations in the spleen, or clinical aberrations in its function, have not been described frequently in the generalized forms of Kaposi's sarcoma. This may be due, in part, to incomplete observation, according to Stats (246) who believes that extreme splenomegaly may be present in this disease. The organ may extend anywhere from the costal margin down to the hypogastrium, to the right of the midline and may occupy the entire left upper abdominal quadrant and considerable segments of the left lower quadrant and epigastrium. There were unquestionable changes in the spleen in three of Stats' four patients and possibly in the fourth. In two cases (cases 1 and 2) the spleen was nodular and fixed to the posterior parietes. In one patient (case 4) the organ was enlarged several times the normal size but was free of tumor. The Malpighian follicles were sharply delimited. The reticulum cell hyperplasia in the pulp was striking, many of the cells were vacuolated or showed degenerative changes. In another patient (case 2) the spleen weighed 700 gms., tumor nodules were not recognized grossly but some hemorrhage was present. Microscopically, however, spindle tumor cells were observed in poorly circumscribed islands infiltrating the surrounding tissue.

Greppi and Bettoni (97) reported moderate shrinkage of the spleen following the subcutaneous injection of epinephrine. Histologic examination of material obtained by splenic aspiration revealed 7 per cent neutrophilic polymorphonuclear leukocytes, 59 per cent mature lymphocytes, 6 per cent histiocytes and 28 per cent monocytes, many of which were immature. However Stats (246 case 1) noted no significant change in the size of the spleen and found an entirely different histologic picture with more lymphocytes and few histiocytes and monocytes.

The pathological appearance of the spleen varies greatly in different cases. In Symmers (254a) case the spleen weighed 100 gms. and the pulp was almost completely replaced by circumscribed tumor nodules. Paolini (169) described a case in which the spleen measured 20 cms. in its longest diameter. The normal architecture was replaced by many young tumor nodules disseminated throughout the organ. There was also myeloid metaplasia and the demarcation between the pulp and Malpighian corpuscles was not distinct.

In some cases of Kaposi's sarcoma with splenomegaly distinct tumor tissue could not be found in the spleen or if present, was not responsible for the enlargement. Greppi and Bettoni (97) found arterial hyperemia, typical of the alterations in hemolytic states. Dalla Favera (52 case 3) found the spleen to be moderately enlarged but without evidence of Kaposi's sarcoma. In the case of Useglio, *et al.* (264) the spleen weighed 1340 gms. and contained many well circumscribed nodules consisting of large phagocytes filled with red blood cells but no tumor tissue was found. In Mierzecki's (169) patient, the spleen was described as follicular. Tumor nodules were found to be responsible for splenomegaly in the case described by Van Cleve and Hellwig (265).

5. Urogenital Tract

Kidneys. In one of Stats (246 case 4) patients, tumor tissue invaded the kidneys at the hilus, accompanying large vessels, and a few flat plaques were apparent under the capsule. In-

volvement of the kidneys was also described by Mierzecki (169) and Van Cleve and Hellwig (265)

Bladder Involvement of the urinary bladder was described by Dillard and Weidman (55) A 76 year old man who had Kaposi's sarcoma for 17 years before the development of hematuria, was described by Smith and Samitz (243) Cystoscopic examination revealed two yellowish nodules on the left bladder wall.

Scrotum. The patient reported by Aegerter and Peale (2) showed involvement of the scrotum.

Penis. There was involvement of the glans penis in the cases reported by Barringer and Dean (13) Greppi and Bettoni (97) Pearce and Walker (192) Roger and Vigne (208) Bluefarb and Webster (24c) and Ronchese and Kern (210b) (See Figs. 16, 17 and 18.)

6. Bone Involvement Occasionally the bony system may be involved. Any part of the bone, including the epiphysis, diaphysis, marrow and periosteum may be affected. The most frequent sites of bone involvement are the hands and feet where the phalanges may be completely destroyed Lesions occurring in the bone may be due to autochthonous origin of the Kaposi's tumor or to direct extension from soft tissue

Bone involvement was first described by Scholtz (226) in 1899 He found considerable decalcification and much destruction of the skeleton of the foot in one patient. The foot was amputated and subsequent histologic examination proved that the bone was riddled with sarcomatous tissue

Aegerter and Peale (2 case 2) reported a 63 year old man who had developed a small nodule on the outer aspect of the left foot three years previously A few months later a similar nodule appeared posteriorly under the lateral malleolus which grew rapidly and apparently fused with the first mass. A similar nodule appeared later under the dorsum of the proximal phalanges of the third and fourth toes. Roentgenograms showed a soft tissue tumor invading the bone Histologic examination revealed Kaposi's sarcoma and the foot was amputated.

The patient, described by Felt (70) was a 53 year old American man whose bone involvement was preceded by lesions in the mouth. One year after onset a few nodules appeared on the instep of the right foot. They were rather firm warty and of a dark brown color A small ulceration occurred following surgical removal of a lesion for histopathologic study This examination revealed Kaposi's sarcoma. The other foot appeared warty and thickened. Cafaffa (34) presented a 20 year old woman who had cutaneous lesions of Kaposi's sarcoma in addition to osteoatrophy of the bones of one foot. A patient who had cyst like areas of rarefaction in the bones of the hand and foot was described by Ronchese and Kern (210a) A 61 year old man with visceral and cutaneous lesions of Kaposi's sarcoma was described by Sherwin and Gordimer (236) Roentgenograms of the right foot and leg, which were the sites of cutaneous tumors, showed considerable demineralization of the bones with what appeared to be a destructive process of the os calcis. The leg was amputated and a longitudinal section disclosed a fungating growth extending from the skin, through the muscles, and into the os calcis.

There is a report of a patient who developed Kaposi's sarcoma at the age of five years who also had osseous changes in the left pubic bone left ilium and humerus (Mississippi Valley and Central States Dermatological Association: 37) Nesbitt, *et al* (178) reported a case of disseminated visceral lesions of Kaposi's sarcoma without cutaneous lesions. At autopsy tumors were found in the thoracic and lumbar vertebrae. Histological examination of the bone lesions revealed a granulomatous hemorrhagic sarcoma with a pleomorphic spindle cell as the dominant structural unit. Roentgen examination of Kusnezow's (142) patient showed definite atrophy of the bone substance within the third to fifth lumbar vertebrae Laterally especially on the fourth lumbar vertebra, were periosteal nodes; in parts, rarefaction in the third lumbar vertebra, narrowing of the intervertebral space between the fourth and fifth lumbar vertebrae and an indis-



60. Cyst-like areas of rarefaction. (Courtesy of Francesco Ronchese. A.M.A. Arch. Dermat. & Syph. 70:31–, 1954.)

tinctness between the third and fourth lumbar vertebrae. Frolich (82) presented a 44 year old man who had skeletal lesions which appeared as areas of rarefaction on roentgenograms.

Destruction of the skull in this disease was described by Kren (139) In this case, the face had become monstrously deformed by a confluent tumor which was as hard as cartilage and localized in the greater part of the face and the left side of the lower jaw After 4,750 roentgen radiation, his face became nearly normal in size. The skin was slightly atrophic, with some enlarged veins, and was faintly bluish. The defects of the skull largely filled out and he felt well. Ramel (203) described a typical nodule at the base of the skull and in the sulcus transversus.

Jacobsen (125) reported a 65 year old Norwegian woman whose lesions were localized on the face. Roentgenograms showed large defects in the frontal and nasal bones. Bone involvement has also been described by Mierzecki (169 case 7) Bernhardt (19) and Pick (196b) Jeanselme, *et al* (128) found bony calcification in their patient. Beek (16) described two cases of Kaposi's sarcoma with well developed elephantiasis and lymphectasiae and lymphocytic infiltration of the lymph follicles. The first patient had a large ulceration which necessitated amputation of the leg and the second developed localization of the bone

7 Heart Involvement There have been several publications in recent years which suggest that Kaposi's sarcoma may exist as a primary tumor of the heart without cutaneous manifestations. According to Stats (246) the tumors are detected either by their size, hemorrhage or irritation of a serous membrane leading to an effusion into a serous sac (pleura or pericardium) as in three of his cases. The fluid is frequently hemorrhagic and may be xanthochromic. There is a tendency toward recurrence Ascites of significant degree have not been described. In one case in Stats series, there were several nodules in the epicardium and myocardium of both ventricles and in another patient, who had extensive lesions, the heart

was spared but several tumor plaques were present at the base of the parietal pericardium. Autopsy in the latter case revealed two firm bluish nodules, 3 mm. in diameter observed through the epicardium near the posterior descending branch of the left coronary artery and a similar nodule near the right coronary artery on the anterior surface of the heart.

Although Weller (275) believes there have been no accounts of primary heart involvement in Kaposi's sarcoma "as such," it is his opinion that it can occur. When the histological description of a cardiac neoplasm is characterized by sarcomatous tissue infiltrated with severe hemorrhage, it is suggestive of this type of involvement. He reports two cases which were diagnosed at autopsy. The first patient, a 30 year old man, first developed cough, yellowish sputum and night sweats, together with edema of the face and mild jaundice. Roentgenogram of the chest revealed a vertical shadow in the right auricular region. Autopsy revealed nearly complete occlusion of the right auricle by a large mass which was firmly attached to the wall. The initial symptoms in the second case, a 26 year old man, were weakness and cough. At autopsy the right auricle revealed a hemorrhagic neoplastic mass. The characteristic physical sign in both cases, according to Weller, was the peculiar edema of the face and neck which, despite the apparently normal texture, appeared wax-like and stretched over an increased amount of subcutaneous tissue.

In three patients described by Choisser and Ramsey (40) the process originated in the skin and one patient died as a result of hemorrhage from a visceral lesion. They believe the neoplasm to be a cancerous representative of vascular tumors and should be designated angiosarcoma while the cutaneous subvariety should be called Kaposi's sarcoma. They found sections from the Cabot case (36) to be identical with their own and, therefore, believe that primary Kaposi's sarcoma of the heart is not rare and attribute previous diagnostic difficulty to lack of proper identification.

Similar cases have been described by Aegerter and Peale (2) and Cuhna Motta (50) although none of these patients

exhibited a distribution of lesions similar to that of classical Kaposi's sarcoma with visceral involvement. In these cases, diagnosis is determined by the histological resemblance of the cardiac tumors with the common cutaneous tumors. According to Hamilton-Paterson and Castleden (107) a so-called pseudomyxoma of the heart may have a similar structure. Stats (246) believes that cardiac involvement in Kaposi's sarcomatosis with cutaneous involvement differs greatly from these cases. He states that neoplastic involvement of the heart in Kaposi's sarcoma is incidental and does not give rise to symptoms.

A 43 year old woman, described by Raw (206) had chest pain, dyspnea on exertion and orthopnea for three and one-half years. Examination revealed ascites, edema of the legs, enlargement of the superficial thoracic veins, dullness of the right chest and hepatomegaly. At autopsy the inferior vena cava, at the entrance to the right auricle, was found to be torn and a hard, 3 by 3 inch, sarcomatous tumor involved the right auricle and extended down the course of the inferior vena cava, terminating on the under surface of the liver as a distinct, hard, nodular mass. Norton's (181) patient, a 29 year old man, developed cough and bloody sputum. He had moderate cyanosis and no cardiac abnormalities on physical examination. Autopsy revealed a tumor which filled the entire left auricle extending down into the mitral orifice which was, histologically Kaposi's sarcoma.

Cardiac involvement in a 33 year old woman who had attacks of substernal oppression and breathlessness for 17 months and cough, fever and chest pains for seven months was reported (Cabot Case 22491 36). The lobulated mass in the right auricular region, demonstrated roentgenologically proved to be Kaposi's sarcoma on histological examination. Cases of this type have also been described by Clerc, *et al.* (42) Binder (23) and Ehrenberg (60).

Cardiac involvement with formation of an auricular thrombus was described by Nesbitt, *et al* (176). Tumor nodules in the epicardium were reported by Symmers (254a) and a

small nodule was present in the subepicardium of the left ventricle in a patient reported by Dillard and Weidman (53). The lesions were limited to the pericardium in Van Cleve and Hellwig's (265) case.

Cardiac neoplasms were also described by Baculoglu, *et al* (9), Crillo (99), Hewer and Kemp (117), Muller (175), Shelburne (235), Smith (242), and Willius (281).

8. Rare Involvement.

Muscles. Muscular lesions appear to be rare and the smooth and striated musculature appear to be resistant to the process. Denzer and Leopold (54) have described involvement of the diaphragm and intercostal muscles and involvement of the psoas muscle was reported by Greppi and Bettoni (97).

There are no reports of uterine involvement. However, Stats (246) described two patients with involvement of the broad ligament near the uterus who had two firm tumor nodules, 3 mms. in diameter, and several similar nodules in the diaphragm.

Central Nervous System. Brain lesions have been reported by Nesbitt, *et al* (176) and Schirren and Burkhardt (224). Involvement of the dura was supposedly present in Denzer and Leopold's (54) case. There has been no report of spinal cord involvement. While fairly typical, Saphier's (219) patient showed extension along the nerve trunk and blood vessels and involvement of the nerve sheath, which was riddled with numerous blood spaces, and extensive infiltration of the connective tissue with spindle and plasma cells. The only other report of this form of extension in Kaposi's sarcoma was by Semenow (231).

Eye Involvement. Ocular involvement is rare in Kaposi's sarcoma. An 84 year old man, presented by Silver (238), developed a red hemorrhagic cyst of the right lower conjunctival sac which was, histologically, reported to be angiosarcoma.

In addition to the classical cutaneous changes of Kaposi's sarcoma, Noto's (182) patient had involvement of both eyes

There were vascular lesions of lacunar type on the bulbar conjunctiva and marked pigmentary deposits, with a soft out line, on the surface of the iris, crossed by several small, dilated vessels.

Adrenal Involvement A distinct, diffuse type of hyperplasia of lipoid-poor cortex was described by Becker and Thatcher (15b) There were many dark brown erosions which tended to follow the mucosal folds in the gastrointestinal tract. However no tumors were detected histologically Adrenal cortex involvement was also described by Stats (246)

E. Associated with Other Diseases

Lymphomas. Contemporary investigators tend to include Kaposi's sarcoma in the "lymphoblastoma" group of diseases. The increasing number of reports of Kaposi's sarcoma associated with members of this group are evidence in support of the relationship of this disease to the reticuloendothelial system. Willis (280) suggested that Kaposi's sarcoma may be a variant of the "lymphoblastomas" with prominent cutaneous lesions related to those of Hodgkin's disease and mycosis fungoides.

Mycosis Fungoides. Histologically confirmed Kaposi's sarcoma which occurred late in the course of mycosis fungoides was reported by Lane and Greenwood (143) The mycosis fungoides, of four years duration, had evolved through the prefungoid stage to the typical tumor stage. Numerous small, round, dome shaped, nonpigmented tumors appeared on the feet and gradually extended up the leg. The previous histologic diagnosis was mycosis fungoides but these tumors showed histological changes typical of Kaposi's sarcoma, with considerably less pigmentation than usual. Post mortem sections revealed Kaposi's sarcoma and typical mycosis fungoides in the same section. Lapowski (146) reported a case in which the lesions on the toes were Kaposi's sarcoma while those on the trunk were mycosis fungoides. Winer (283: case 4) re-

ported a 76 year old woman who had mycosis fungoides and Kaposi's sarcoma.

Hodgkin's Disease A 65 year old man who had hepatosplenomegaly lymphadenopathy remittent fever weight loss and slight leukocytosis for four years, was described by Goldschlag (90) The diagnosis was malignant lymphogranulomatosis. Pigmented raised nodules appeared on the lower extremities and right side of the thorax three and one-half years after the onset of symptoms. The gross and microscopic characteristics of these nodules indicated Kaposi's sarcoma. Goldschlag presumed that the occurrence of two lymphatic system diseases in the same patient was the result of the same stimulus. Talbott (256) described a 56 year old woman with Hodgkin's disease in whom superficial lymphadenopathy was preceded by evidence of Kaposi's sarcoma of the skin. The chronological association of the two diseases was fairly close but the etiologic association is difficult to establish.

A 54 year old man who developed Hodgkin's disease nine months before the appearance of cutaneous lesions of Kaposi's sarcoma, is reported by Greenstein and Conston (96) The pathologic diagnoses at autopsy were 1) Hodgkin's sarcoma of the spleen, lymph nodes and bone marrow with pulmonary and renal infiltrations, and 2) Cutaneous angio-endothelioma (Kaposi's sarcoma with lymph node and pulmonary metastases) It is their belief that the two conditions present in this patient are histogenetically related and that possible other coincident occurrences of these two lesions have not been fully appreciated and recorded.

Osborne *et al* (187 case 7) reported the association of Kaposi's sarcoma and Hodgkin's disease in a 67 year old woman. This association has also been observed by McCarthy and Pack (153) Erf (68) and Wolf (259)

Lymphosarcoma A patient having Kaposi's sarcoma which developed into lymphosarcoma was reported by Bellord (18) McCarthy and Pack (153) described two cases of Kaposi's sarcoma, one of which was associated with Brill Symmers

disease and the other with lymphosarcoma. Higgins (118) reported Kaposi's sarcoma of the skin and lymphosarcoma of the lymph nodes. He believes this does not represent a separate disease entity but rather another of the varied manifestations of Kaposi's sarcoma.

Bluefarb and Webster (280) reported Kaposi's sarcoma associated with lymphosarcoma (see Fig. 2.) This 78 year old Negro had been hospitalized on several occasions because of lymphosarcoma of the lymph nodes. Following roentgen ray therapy to the cervical, sternal and abdominal areas, the lymph nodes gradually decreased in size, and his general health improved. Seven months later he developed swelling of, and a few nodules at the base of the penis. Several months later a small "bump" appeared on the right thigh. There were numerous reddish-brown to blue nodules varying from 1 mm. to 2 cms. in diameter. Some were slightly indurated and this induration extended to the right inguinal area and fused with the slightly enlarged inguinal lymph nodes. The skin was somewhat hyperpigmented in the involved area. There was a diffuse swelling of the penis with a few small indurated papules at the base and hyperpigmentation of the overlying skin. Two hyperpigmented patches, with central crusting, were present above the left knee, anteriorly. A moderately enlarged lymph node was present in the right axilla.

Lymphatic Leukemia. Cole and Crump (44) described a 63 year old man who had numerous, irregularly shaped areas of brownish red and bluish red pigmentation scattered over the entire body and most marked on the extremities. This condition progressed for three years until the papillomatous over growths on the lower legs and left foot made walking impossible. At this time, blood studies revealed lymphatic leukemia although the cutaneous lesions were never characteristic of leukemia but were always distinctive of Kaposi's sarcoma. The patient recorded by Hufnagel and Dupont (123) was a 75 year old man who had numerous lymphoid nodules associated with the vascular lesions of Kaposi's

sarcoma. Histologic evidence of Kaposi's sarcoma and lymphatic leukemia in the same lesion is described by Sachs and Gray (217b). An eruption, consisting of irregularly shaped violaceous plaques, 1 to 4 cms. in diameter had been present on the left sole, instep and inner aspect of the heel for seven months. Histologic examination revealed Kaposi's sarcoma in the middle and upper layers of the cutis and lymphatic leukemia in the deep cutis. The clinical features of Kaposi's sarcoma and the hematological picture of leukemia were present in all three of these patients and all three died of leukemia rather than of Kaposi's sarcoma.



61. Kaposi's sarcoma associated with lymphatic leukemia.
62. Kaposi's sarcoma associated with lymphatic leukemia.

The simultaneous occurrence of Kaposi's sarcoma, lymphatic leukemia and diabetes is described by Fischer and Cohen (74). The patient, a 74 year old man, had Kaposi's sarcoma for 25 years while the leukemia developed later.

We have observed a patient having Kaposi's sarcoma and lymphatic leukemia who had involvement of the fingers and toes. This man died of lymphatic leukemia rather than of Kaposi's sarcoma.

Myeloid Leukemia. The association of myeloid leukemia and Kaposi's sarcoma was reported by Tedeschi, *et al.* (257)

This patient, a 65 year old woman, had numerous purpuric areas scattered over the trunk and arms. The Kaposi's sarcoma consisted of a mediastinal mass composed mainly of endothelial-lined sinuses and of impervious or canalized endothelial sprouts. These structures were embedded in a fibrocellular stroma which displayed widespread proliferation of reticulum cells and fibers, fibroblasts and immature hepatic cells. There were concomitant red blood cell extravasations, and blood pigment was noted in places.

Cuilleret and Gallet (51) reported a case of Kaposi's sarcoma with myeloid leukemia in a 74 year old Italian man. The peripheral blood count showed 45 per cent polymorphonuclear leukocytes, 22 per cent metamyelocytes and 6 per cent myelocytes. The sternal bone marrow examination revealed 57.5 per cent neutrophils consisting of 13.5 per cent polymorphonuclears, 20 per cent metamyelocytes 15.5 per cent myelocytes and 8 per cent promyelocytes.

Carcinoma A 67 year old woman, described by Stats (246) had nodules of Kaposi's sarcoma affecting both lower extremities. At autopsy a firm, ulcerated, fungating adenocarcinoma was found in the sigmoid colon. Ebert and Otsuka (59) presented a 70 year old man who had Kaposi's sarcoma involving the toes and dorsa of the feet in addition to carcinoma of the rectosigmoid region of the colon. The 73 year old man, reported by Binder (24) had an adenocarcinoma of the stomach, which was removed surgically and approximately six months later developed Kaposi's sarcoma of the right ankle. Dillard and Weidman (53) described Kaposi's sarcoma associated with an hypernephroma. Andrews (6a) and Carpino and Secchi (35) have reported Kaposi's sarcoma associated with fibrosarcoma. Abramowitz (1) described a 60 year old man who had Kaposi's sarcoma and osteogenic sarcoma of the tibia. Philippson's (197) patient had Kaposi's sarcoma associated with widespread carcinoma which was primary in the liver The patient reported by Silver (238) had Kaposi's sarcoma, diabetes and epithelioma of the face.

We observed a 54 year old Italian woman who had Kaposi's

sarcoma and adenocarcinoma. The lesions on the right leg, which had been present for three years, were pigmented and there was one crusted, purplish nodule the size of a cherry. The uterus had been removed surgically four years previously because of adenocarcinoma of the cervix.



63. Kaposi's sarcoma in a patient with carcinoma of the cervix.

Other Diseases. Kaposi's sarcoma associated with von Recklinghausen's disease of the skeletal and nervous system was described by Roger and Vigne (208).

A patient having Kaposi's sarcoma of the legs and lupus vulgaris involving the nose was reported by Eller and Kest (63). A case of Kaposi's sarcoma associated with hidradenitis suppurativa was presented by Blumenthal, *et al.* (27).

Diabetes Mellitus. An incidence of 46 per cent diabetes mellitus, or six of 13 patients having Kaposi's sarcoma, was noted by Hurlbut and Lincoln (124). Two of these patients were known to be diabetic prior to the diagnosis of Kaposi's

sarcoma and the other four showed evidence of diabetes following the appearance of the cutaneous lesions. They believe that patients with Kaposi's sarcoma should be studied for possible diabetes. The reason for the coexistence of the two diseases was not apparent, and they found the administration of arsenic did not appear to affect the cutaneous lesions. The possibility of an endocrine imbalance is suggested in one instance (124, case 2) and although a diagnosis of diabetes was not made in this case, the results of the glucose tolerance test and the patients utilization of high doses of insulin suggested the presence of an abnormal anti insulin factor Definite clinical improvement followed the onset of "spontaneous feminizing changes. Since this disease occurs much less frequently in women, they believe further study from an endocrinologic standpoint, should be done.

Fischer and Cohen s (74) patient, a 72 year old man with Kaposi's sarcoma of the extremities of 24 years duration, subsequently developed lymphatic leukemia and diabetes mellitus. The patient described by Silver (238) had Kaposi's sarcoma and diabetes.

VI

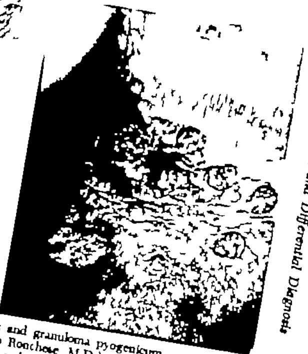
DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

THE CLINICAL diagnostic features of Kaposi's sarcoma, as outlined by Ronchese and Kern (210b) are 1) The disease occurs most commonly in men, 2) The greatest incidence is in the sixth and seventh decades of life, 3) The extremities are predominantly involved, 4) The distribution is usually symmetrical, 5) The lesions consist of bluish, bluish red or reddish brown nodules and plaques, 6) The lesions are painless and ulceration is uncommon, 7) Edema of an extremity is common, 8) The residual atrophy and pigmentation of the lesions involute spontaneously 9) The course of the disease is slow and 10) There is no change in the patient's general condition until late in the disease.

The numerous diseases to be considered in the differential diagnosis depend upon the characteristic feature, or features, which are present. Although the clinical picture is very typical in this condition, it has occasionally been mistaken for Boeck's sarcoid, xeroderma pigmentosum, acanthosis nigricans, lichen planus, granuloma pyogenicum, glomus tumor syphilis, leprosy angiomas, angiokeratosis mycosis fungoides and metastatic lesions.

Symmers (254a) believed the telangiectatic purpuric hemorrhagic and simple inflammatory processes should be differentiated in the early phase of Kaposi's sarcoma, before the occurrence of extensive hyperplasia. Telangiectasia, he continues, is not related to hyperplasia of blood and lymph vessels. New vessels, particularly capillaries, are present in hyperplasia, while there are dilated, tortuous vessels in telangiectasia. Hemorrhage is not a differential point in the early course





64 Lesions resembling angiomas and granuloma pyogenicum (Courtesy of Francesco Ronchese, M.D.)

65 Lesions resembling angiomas and granuloma pyogenicum. (Courtesy of Francesco Ronchese, M.D.)

of Kaposi's sarcoma unless combined with other features of the disease. A concentration of cytology plasma cells, angioblasts and spindle cells is important since these cells together with vascular hyperplasia and hemorrhage, do not occur in a simple inflammatory process.

According to MacKee and Cipollaro (155b) the clinical diagnosis can usually be quickly and easily established, except in various stages of evolution when the disease may simulate



68 Lesions resembling angiomas and granuloma pyogenicum. (Courtesy of Francesco Ronchese, M D)

lichen planus, mycosis fungoides, syphilis, sarcoidosis, or leprosy Lichen planus, particularly the hypertrophic type, closely simulates the lesions of Kaposi's sarcoma. Lesions occurring in the prefungoid stage of mycosis fungoides resemble various scaly and exudative dermatoses but the lesions have no predilection for the extremities. Syphilis is differentiated by the history distribution of lesions, raw ham color response to therapy and serology Although sarcoidosis may simulate Kaposi's sarcoma for a time, this condition presents no infiltrated plaques, vascular elements visceral lesions or definite predilection The brown colored lesions present in leprosy

have a slower evolution and a long incubation period. The anesthesia present in leprosy is never encountered in Kaposi's sarcoma.

With definite hyperplasia of the vascular connective tissue or other cellular elements, some of the granulomas and neoplasms must be excluded, according to Sachs, *et al.* (217a) Tuberculosis may be excluded by the absence of epitheloid and giant cells and tubercles. Syphilis can be eliminated by the presence of angioblasts and spindle cells and the absence of vascular changes and plasma cell collarets. There is a difference in the development and evolution of granulation tissue which terminates in complete fibrosis and there are cells which are not present in Kaposi's sarcoma. There is usually an abundance of fibroblasts and plasma cells, while angioblasts are scarce and there are no spindle cells. They believe the most frequent and important neoplasms to be considered are angioma, angiosarcoma, spindle cell sarcoma, glomus tumor granuloma pyogenicum and circumscribed lymphangioma. The common, typical angiomas cause little diagnostic difficulty unless there are cellular elements such as angioblasts. They believe this type of angioma is frequently referred to as endothelioma or perithelioma, although they are in agreement with those who question the term perithelioma and believe them to be angiomas associated with angioblasts. The differential diagnosis of these angiomas is established by the absence of hemorrhage and spindle cells. A positive Perls reaction, plasma cells and increased lymphatic vessels and spaces does not occur in angiosarcoma. Lacking these features, Kaposi's sarcoma is differentiated from angiosarcoma only by proper diagnosis of the initial lesion. There is little difference between spindle cell sarcoma developing from Kaposi's sarcoma or from an unrelated condition. The proper diagnosis may occasionally be established by the presence of angioblasts and plasma cells. Corroborating evidence of Kaposi's sarcoma, such as the clinical picture and history may establish the diagnosis.

Histologically glomus tumors show the capillaries, even in

the form of angiomata, to have a surrounding, intense, uniform focal infiltration of angioblasts. Other types of cells are not found. The participation of nerve and muscle tissue in this process is not stressed, according to Sachs *et al.* (217a) They state that typical areas of glomus tumor are found histopathologically in clinical and microscopically proved cases of Kaposi's sarcoma. Proper diagnosis can be established only by careful study of the entire section. A positive Perls reaction generally occurs in Kaposi's sarcoma. Although it should be presumed that hemosiderin would also be present in glomus tumors and granuloma pyogenicum, they were able to demonstrate its presence in only a small percentage of cases.

The patient described by Klaber (135a) appeared to have some clinical features of acrodermatitis chronica atrophicans or of anetoderma erythematodes of Jadassohn although the absence of definite elastic atrophy did not favor a diagnosis of either of these related conditions. This patient, a 56 year old man, had developed erythema and edema of the back of the hands six years previously. There were several circumscribed, scaly edematous areas involving the dorsum of both feet and lower legs. There was an intense erythematous edema of the backs of the hands and fingers and similar although smaller discrete lesions on the flexor aspect of the wrists and forearms.

Gilchrist (87a) observed a man having a typical rosacea of the nose which proved to be Kaposi's sarcoma on histological examination. Lesions appeared on the extremities a few years later and the case became one of classical Kaposi's sarcoma.

A 62 year old man, described by Niles (179) had developed a flat, purplish red area on the lower leg 20 months previously. This lesion gradually enlarged, became hard, elevated and warty simulating hypertrophic lichen planus. Bancroft's (11) patient was a 69 year old man whose initial lesions occurred on the left ankle and later involved both legs. The lesions appeared lichenoid and simulated lichen planus. A similar case simulating hypertrophic lichen planus was presented by

Cornbleet (46) Zeisler (290) stated that this resemblance is sometimes striking and he had observed two patients having typical Kaposi's sarcoma who were being treated for lichen planus.

Although granuloma pyogenicum and Kaposi's sarcoma present similar vascular changes, the cytology differs. There are numerous, diffusely arranged angioblasts plasma cells are not prominent except in secondarily infected lesions, and there are no spindle cells. There is little tendency toward fibrosis in granuloma pyogenicum Wigley (278) described a 43 year old woman who developed a painful, red, semi-solid "angiomatous tumor on the "ball" of the foot. This lesion, of filbert nut size, was flush with the skin surface and simulated granuloma pyogenicum. The 49 year old man, reported by Becker and Obermeyer (15a) had recurrent erythematous, elevated tumors on the chin for four or five years Despite cauterization, the lesions recurred. Some of the lesions were pedunculated and appeared to be typical of granuloma pyogenicum.

VII

PROGNOSIS

Some investigators, including Kaposi (132a) believe this disease to be fatal in two to three years while others are of the opinion that the duration may be eight to ten years, and rare cases may survive for 20 or more years.

Severe, rapidly progressive cases, having a sudden fatal outcome have been described, particularly by Italian observers. From the reports it would appear that this disease has a more violent course among Southern Europeans. Hansson (103) believes the tumors are more malignant in younger than in older persons, although his evidence was not conclusive

The prognosis should be guarded, according to McCarthy and Pack (153) since long remissions are quite deceptive to both patient and physician. It is difficult to evaluate the aggressiveness of the tumor for many months and deceptive remissions and bizarre variations may occur in women They also mention unusual racial influences the fulminating type being extremely rare in Scandinavians and frequent in Italians and Jews. Generally the prognosis is not favorable when there is rapid tumor involvement of both extremities, associated with edema, or when primary or secondary lymph node or visceral involvement occurs They found no relation of the age of the patient to the clinical activity of the disease and death usually resulted from progressive cachexia, intercurrent infection, or hemorrhages from friable bulky tumors in the gastrointestinal tract or lungs Septicemia and gangrene following radionecrosis, may also be the chief cause of death.

Among 36 patients studied by McCarthy and Pack (153) 28 were living and only seven were free of the disease Three

had been well for five, six and nine years, respectively: a definite "cure" rate of 19 per cent of patients treated more than five years previously. Four of the group of 26 living patients, however, had survived 10, 11, 12 and 25 years with active disease. All had received radiation therapy. In the series of patients who died of the disease, three had survived five to ten years, and two had lived for 15 to 20 years. One of these patients died of prostatic cancer six years after the initiation of therapy for Kaposi's sarcoma. The average survival interval, with treatment, was approximately eight years.

The variation in duration appeared to be dependent on the age of the patient in the cases studied by Dorffel (56). The younger and older age groups had a more rapid and progressive course. He noted many recorded cases of 25 years duration and found the duration to be from eight months, as described by Mariani (160), to 25 years, as reported by Prokopcuk and Cutalova (200). He also found that the race of the patient had no bearing on the prognosis. Most patients died as a result of prolonged progressive wasting and emaciation, although some died of intercurrent disease.

The course is ordinarily slow and steadily or intermittently progressive, according to MacKee and Cipollaro (155b), who give the duration as one to 25 years, with a five year average. Choisser and Ramsey (40) found the duration to be six months to two years in the 13 fatal cases recorded in a seven year period. Death may occur from infiltration of the lungs, liver or spleen, but involvement of the intestinal mucosa with ulceration causing hemorrhage and exsanguination is much more frequent, according to Aegerter and Peale (2). When the tumor is primary in the viscera, cutaneous tumors usually are not present.

The disease ran an extremely rapid course in a 63 year old woman described by Symmers (252a). Kaposi's sarcoma involved the greater portion of the upper extremities and appeared as scattered nodules on other body surfaces, including the face and scalp. Death, resulting from intercurrent causes, occurred one month after the appearance of cutaneous nod

ules. Although Symmers had never known Kaposi's sarcoma to occur in a patient with jaundice, he suggests that hemorrhage into the nodules may have been encouraged or initiated by bile salts.

Kaposi (132a) described patients who died after two to six, or eight years, who exhibited secondary deposits in the internal organs, particularly the large intestines. However many cases having a similar onset have been reported which were observed for long periods and did not prove fatal. In one such case, described by Brayton (29) the patient had been well for 25 years and MacKenzie's (156) patient was well 15 years after onset of the disease, although the local severity of the disease had necessitated amputation of one leg. A 70 year old man, reported by Silvers (239a) had the disease for 15 years. Estrin's (67) patient, a 68 year old man, had edema of the leg for 35 years but the condition had been painful only for the first 10 years. Two years before examination, nodules developed on the left foot and spread slowly to involve the entire leg. Estrin does not believe this 35 year duration to be unusual in Kaposi's sarcoma. Sulzberger (253) reported a case of 18 to 20 years duration and Zakon's (289a) patient had the disease for 25 years. A 53 year old man, described by Highman (120a) had lesions of Kaposi's sarcoma for 23 years. The 53 year old Greek man, reported by Akwa, *et al* (4) had Kaposi's sarcoma for 13 years and two of Hansson's (103) patients, who developed the disease before they were 50 years of age had been symptom free for 10 and 24 years respectively.

Kaposi (132a) believed spontaneous healing of the tumors was due to hemorrhage and fibrin deposits with subsequent organization and contraction. However Philippson (197) and Dalla Favera (52) believe that hemorrhages are not directly related to involution of the tumors and fibrin deposits rarely occur. Gilchrist and Ketron (87b) suggest that the involution is due to gradual blocking of the small arteries, supplying the lesions with sclerotic processes. They believe the more vegetative the growth, the greater is the amount of blood

required. As the blood supply is decreased, the tissue gradually reverts to the more resistant fibrous type with complete involution occurring later in some cases. In cases having a narrowed source of blood supply as in pedunculated tumors, degenerative changes may occur in the new growth.

A case of "Pigmented Neoplasm of the Skin" was described by Hardaway (109a). The patient had multiple cutaneous tumors for ten years which were histologically alveolar sarcomata. The general health was not affected. A later report (109b) states that the patient was in good health 15 or 16 years after onset of the disease and the sarcomatous tissue had undergone involution resulting in a nearly atrophic condition of the skin. The patient reported by Miller (170) had developed many lesions of Kaposi's sarcoma of the feet, hands and ears about 10 years previously. Three years later a severe streptococcic infection of the upper arm developed, with fever of 106 to 107 deg. F for a considerable period of time. Two months later the Kaposi's sarcoma lesions began to disappear and within five months were entirely gone. Six years later there was no recurrence. Forman's (79c) patient, who had the disease for 28 years, showed a marked tendency to spontaneous cure.

The prognosis of Kaposi's sarcoma appears to be unfavorable despite the fact that spontaneous cures, especially clinical cures following therapy, have been reported. Spontaneous healing was noted by Bernhardt (19), Brayton (29), Dalla Favera (53), Gilchrist and Ketron (87b), Hansson (108), Heimann (115), Kaposi (132a), MacKee (155a), Philippson (197), Sellei (230), Wise (266a) and others.

Despite the numerous reports of disappearance of the lesions, without recurrence, MacKee and Cipollaro (155a) believe that eventual recurrence is the rule. The treated eruption may undergo involution but there is little or no influence on the cause of the disease and it does not prevent the development of new lesions on other areas of the body. Although irradiation may occasionally appear to result in a seemingly permanent regression, Kulchar (141) believes there are usually recurrences.

VIII

TREATMENT

R*adiation Therapy* There is general agreement that roentgen ray therapy is the method of choice in the treatment of Kaposi's sarcoma since the lesions are relatively radio-sensitive. This therapy is particularly effective if the lesions are multiple or if the process is diffusely extensive.

The early more vascular macules and nodules are far more radiosensitive than the older infiltrated plaques, according to McCarthy and Pack (153). These early lesions will usually regress completely when treated with unfiltered low voltage roentgen rays (one to two threshold skin erythemas). For larger superficial areas, unfiltered low voltage doses (100 kilovolts, 20 to 30 cm target skin distance and small portals) for an average of 400 to 800 roentgen individual doses, is suggested. They found that larger doses, with some filtration, were required for bulky skin plaques. High voltage roentgen rays were administered to deep tumors which involved lymph nodes, mediastinum, lungs, abdominal viscera and bone. In two patients having the disease in the os calcis and tibia, the tumors regressed and pain disappeared following 200 kilovolts of roentgen rays. However, with the exception of one dramatic regression in the treatment of splenomegaly, they found high voltage roentgen ray therapy only moderately successful. They strongly emphasize that radiation therapy should be administered in conservative doses if the sarcoma is extensive or edema is present, since the blood supply is usually impaired. Overtreatment may cause necrosis, infection and gangrene. Interstitial radiation and "blanket radiation" with large portals are hazardous for the same reason.

The cutaneous lesions of Kaposi's sarcoma are occasionally

recalcitrant but usually respond favorably to doses of roentgen rays which can be administered with safety according to Mackee and Cipollaro (155b) Large doses should not be administered over large areas, especially to young or middle aged patients, until more conservative measures have been tried. The production of erythema should be avoided. They suggest treatment of the cutaneous lesions with 75 r once weekly to all areas involved in the process. Four to 12, or occasionally 16 treatments may be required and this amount should not, ordinarily produce erythema. Superficial lesions, not too thick, are treated with 80 to 100 kilovolts unfiltered radiation. In cases of unusually resistant eruptions, radiation should be discontinued and arsenic given for several months, after which a single erythema dose (300 r) or a larger dose, may be administered to small lesions. Larger doses may be used for small lesions since the area may be excised in the event of injury and the effect is less than in large areas where secondary and particularly scattered radiation must be considered. The effect is approximately 25 per cent greater for a four square inch area than for an area of one square inch, according to MacKee and Cipollaro. Therefore it may be safe to give a so-called erythema dose, or even a much larger dose, to a pea size nodule but unwise to administer this amount to a large area. Some pigmentation may persist for many months following resolution of the eruption or there may be atrophy and possibly telangiectases. They suggest the use of filtered radiation, usually 3 mm. of al., with no change in the dosage scheme for the treatment of thick lesions. They believe that irradiation in Kaposi's sarcoma acts in much the same manner as in mycosis fungoides, a condition which eventually ceases to be benefited by irradiation. This fact has not been observed in Kaposi's sarcoma.

Guarini (103) described 30 cases of Kaposi's sarcoma treated with roentgen rays and he considered the results to be very good. Hansson (108) treated 23 patients solely with radiation. He employed roentgen rays to large widespread lesions and infiltrations and radium by implantation or ap-

plication method to single tumors. Twelve patients were treated with roentgen rays varying between 1000 and 4000 r the smaller doses given to a larger field. Treatment was administered daily in doses of 300 to 500 r each. Five patients were given filtered radiation (1 mm. al., 100 kv., distance 23 to 50 cm.) In the other cases, 4 mm. Al. or one half mm. Cu. *and 1 mm Al were used as filters, 150 to 180 Kv 23 to 50* cms. distance. The amperes varied from 4 to 6 milliamperes. Some more resistant cases were given a second similar series of treatments two or three months later There was a dry although never desquamative, epidermitis in a few cases. All the tumors treated by this method disappeared with the exception of two cases, having insufficient follow up observation, although they showed definite signs of receding.

Kulchar (141) believes small doses, of about 75 r should be given at weekly intervals, although larger amounts of filtered radiation may be required for more deeply infiltrated lesions. Fox (80b) stated that he had better results with filtered, than with unfiltered, radiation. According to Kren (139) the best therapy is roentgen irradiation, given alone or in combination with arsenotherapy

McCarthy and Pack (153) found that one to two threshold skin erythemas of unfiltered low voltage roentgen rays produced a similar response to that obtained with one to two threshold erythema doses with radium plaques at 1 cm distance.

Small lesions will respond to beta and gamma rays of radium just as they do to roentgen rays according to MacKee and Cipollaro (155b) Beta rays are seldom used except for very superficial lesions with never less than 0 1 mm. Al. Lightly filtered (1 mm. brass, 1 mm. al) gamma rays are satisfactory for most small lesions with the applicator in contact with the surface or at a distance They believe however that radium and radon therapy are not generally satisfactory for Kaposi's sarcoma because of the numerous lesions and large areas to be treated

Five of Hansson's (108) patients were treated by implanta

tion or surface application of radium. For implantation, he used needles with 10 mg. of radium element, with about 1 cm. active length and a 5 cm. distance between the needles. The infiltration was equivalent to 1 mm. of lead and the dose varied between 10 to 40 mg. radium element for two and one-half to four hours. For surface application, the dose was 150 mg. radium element for three hours, distance 12 mm., infiltration equivalent to 3 mm. of lead. All tumors treated disappeared. He believes that if the tumors and infiltrations are multiple and the area of involvement large, roentgen ray therapy is preferred, but single nodules may be treated by implantation or surface application of radium. His investigations revealed no factors which might prove one method more efficacious than the other However he makes one reservation in regard to radium implantation in tumors of the legs and feet, since one patient developed necrosis following a moderate dose.

Hare, *et al.* (110) employed high energy cathode rays for treatment of cutaneous lymphomas and Kaposi's sarcoma. They believe the clinical advantages of this type of therapy to be the possibility of selecting the desired electron penetration by control of the voltage the complete absence of damage to tissues beyond the well defined election range and the reduced biologic effect in the outer layers of radio-sensitive skin

Ultraviolet Light Therapy Jacobsen (125) believes that treatment with Finsen light and quartz light, have given encouraging results.

Surgical Therapy. There has been little reference to, or experience with, the surgical treatment of Kaposi's sarcoma. McCarthy and Pack (153) had gratifying results with wide surgical excision of early solitary lesions. Among seven patients who were free of the disease five had excision of the lesion at the onset of the disease. One patient was well after nine years and two patients whose primary macule of the penis had been treated by amputation, were well for five and





67a. Cutaneous lesions of the foot before cathode ray therapy
(Courtesy of Francesco Ronchese, M.D.)
67b. Cutaneous lesions of the foot following cathode ray therapy
(Courtesy of Francesco Ronchese, M.D.)

six years, respectively. Surgery is contraindicated in cases having extensive multiple tumors or if there is an associated edema. Such edema usually indicates deep vessel involvement and predisposes the tissues to infection and indolent postoperative defects. Fungating tumors of the oral cavity may occasionally be removed by palliative cautery excision and should be followed by intraoral roentgen ray therapy.

Small lesions may be removed with the scalpel or with the cutting current, or they may be destroyed with electrodesiccation, electrocoagulation or other forms of electrosurgery according to MacKee and Cipollaro (155b). Neither excision nor electrocoagulation prevents recurrence or spread, according to Jacobsen (125), although surgical intervention may be indicated in cases of suppuration, gangrene or extensive destruction of the bone.

Chemical Therapy. Nitrogen mustard has proved disappointing in the few patients treated thus far, as mentioned by Osborne, *et al.* (187), Seagrave (228) and Wintrobe and Huguley (284).

Michelson (168) reported failure with urethane therapy for Kaposi's sarcoma.

Although penicillin has been reported of value in the treatment of Kaposi's sarcoma by Grinspan (100) and others, we have had no success with the administration of penicillin, or any other antibiotic, in the treatment of this disease.

Bloom (25b) reported that two patients treated with antireticular cytotoxic serum of Bogomolets failed to respond to therapy. Treatment with Chloroquin and steroids has recently been advocated but the results do not appear to be favorable.

Arsenical Therapy. Arsenic in the form of solution of potassium arsenite or the intramuscular injection of solution of sodium arsenate is occasionally effective and should be used as an adjuvant to irradiation, according to Kulchar (141). Jacobsen (125) also believes arsenic, in the form of neoarsphenamine, often appears to be noticeably effective in causing the cutaneous lesions to disappear and in preventing local recurrence.

Although many believe arsenic therapy to be of value, some consider it to be of questionable value. This treatment was used more frequently in the past than today and Mackee and Cipollaro (155b) found no statistics, based on a reasonably large number of cases, with an adequate observation period, which showed impressive results. However many patients in the past were undoubtedly benefited by this treatment. This drug should be used, they believe, together with roentgen ray therapy or in the event the latter fails. Arsenic is usually administered orally either as Fowler's solution or Asiatic pills, and also by subcutaneous, intramuscular and intravenous injection. Results are approximately the same with the various methods of administration. Best results are obtained by intensive treatment, they believe, and they prefer the subcutaneous injection of 2 per cent sodium arsenate, daily if possible, beginning with one drop and increasing one drop at each injection until a dose of 20 or more drops is reached. A rest interval of at least one month is then given. This treatment is given in courses in accordance with indications and the patient is carefully observed for evidence of intolerance. Contraindications and warning signs are albuminuria, jaundice, diarrhea and other gastrointestinal symptoms, cachexia, marked anemia, congestion of the eyes and any new cutaneous eruption not attributable to Kaposi's sarcoma.

In summary nearly all modalities of therapy including excision with scalpel and cautery, radium pack, external and internal radon, contact roentgen rays and 100, 200 and 210 kilovolt roentgen rays, ultraviolet rays, arsenic, antibiotics and steroids, have been tried without marked success, in the treatment of Kaposi's sarcoma.

REFERENCES

1. Abramowitz, E.W. Kaposi's sarcoma with osteogenic sarcoma of the tibia. *A.M.A. Arch. Dermat. & Syph.*, 7:253 (Feb.) 1923.
2. Aegerter, E.E. and Peale, A.R. Kaposi's sarcoma, a critical survey. *Arch. Path.*, 34:413 (Aug.) 1942.
3. Acosta, G. Etiology and pathogenesis of so-called cutaneous sarcomatosis. *Clin. Chir.* 39:511, 1936. Abst. *Am. J. Cancer* 32:299, 1938.
4. Akwa, C.M.L., Kanter, J. and Marrison, L.S. Multiple idiopathic hemorrhagic sarcoma; case report. *Urol. & Cutan. Rev.*, 54:167 (Mar.) 1950.
5. Andervont, H.B. and Dunn, T.B. Effect of castration and sex hormones on the induction of tumors in mice with o-aminoazotoluene. *J. Nat. Cancer Inst.*, 7:455 (June) 1947.

6a. Andrews, G.C. A case for diagnosis (Kaposi's sarcoma?). *A.M.A. Dermat. & Syph.* 26:549 (Sept.) 1932.

b. Andrews, G.C. Multiple idiopathic hemorrhagic sarcoma of Kaposi. *Ibid.* 38:452 (Sept.) 1938.

c. Andrews, G.C. *Diseases of the Skin*, Ed. 4. Philadelphia, Saunders, 1954, p. 628.

7. Arauz, S., Perrano, J. and Morto, D. Un caso de sarcomatosis de Kaposi con metastasis precoces bucofaringeas. *Semana med.*, 1:1784 (June 7) 1934.
8. Babes, V. I. Ziemssen's *Handbook der speciellen Pathologie und Therapie*. Leipzig, F.C.W. Vogel, 1884, vol. 14, part 2, p. 473.
9. Bacaloglu, C., Lungu, C. and Bailzanu, G. Les thrombus myxoides du coeur. *Presse med.*, 41:2074 (Dec. 20) 1933.
10. Balzer, F., Merle, P. and Duval, R. Sarcomatose primitive multiple de la peau. Rectification de diagnostic. *Bull. Soc. franc. dermat. et syph.* 18:12, 1907.
11. B...schoft, L. Multiple idiopathic hemorrhagic sarcoma (Kaposi). A.M.A. *Arch. Dermat. & Syph.*, 49:295 (Apr.) 1944.
1. Banerjee, B.N. Kaposi's idiopathic hemorrhagic sarcoma. A case in Hindu. *Brit. J. Dermat.* 67:218 (June) 1955.
13. Barringer, B.S. and Dean, A.L., Jr. Kaposi's disease of the penis, report of two cases. *J. Am. A. Genito-Urin. Surgeons*, 28:409, 1935.

14. BECHET, P.E.: Kaposi's sarcoma with unusual features. *A.M.A. Arch. Dermat. & Syph.*, *18*:321 (Aug.) 1928.

15a. BECKER, S.W. AND OBERMAYER, M.E.: A case for diagnosis (granuloma pyogenicum? angiomatous fibroma? benign infectious angioma? Kaposi's sarcoma?) *Arch. Dermat. & Syph.*, *31*:746 (May) 1935.

b. BECKER, S.W. AND THATCHER, H.W.: Multiple idiopathic hemorrhagic sarcoma of Kaposi, historical review, nomenclature; and theories relative to the nature of the disease with experimental studies of two cases. *J. Invest. Dermat.*, *1*:379 (Oct.) 1938.

16. BELK, C.H.: About the angio-reticulomatosis Kaposi. *Dermatologica*, *107*:433, 1953.

17. BELLMAN, H. AND TAVA, L.: Kaposi's multiple idiopathic hemorrhagic sarcoma. *Arch. Dermat. & Syph.*, *44*:93 (Nov.) 1941.

18. BELLONI, L.: Maladie de Kaposi a evolution lymphosarcomateuse. *Ann. Dermat. et Syph.*, *9*:45, 1949.

19. BERNHARDT, R.: Sarcomata idiopathic multiplica pigmentosa cutis (Kaposi). *Arch. f. Dermat. u. Syph.*, *49*:207, 1899. Weitere Mittheilungen uber sarcoma idiopathicum multiplex pigmentosum cutis. *Ibid.*, *62*:237 and *62*:239, 1902.

20. BERNSTEIN, E.T.: Kaposi's sarcoma coincidental with pigmented nevus. *Arch. Dermat. & Syph.*, *60*:443 (Sept.) 1949.

21a. BERTACCINI, G.: Sopra un caso di sarcoma idiopatico di Kaposi (angio-endothelioma cutaneo). *Gior. ital. mal. ven. della pelle*, *61*:580, 1920.

b. BERTACCINI, G.: Studio istologico sopra una forma particolare e poco commune di rammollimento dei noduli nel sarcoma idiopatico di Kaposi (angio-endothelioma cutaneo). *Ibid.*, *65*:1132, 1924.

c. BERTACCINI, G.: Ancora sulla sarcomatosi cutanea di Kaposi (angio-endothelioma cutaneo di Radaeli) Ricerche su quattro nuovi case. *Gior. ital. di derm. e sif.*, *80*:631, 1939.

22. BILANCIONI, C.: Sarcoma di Kaposi con manifestazioni faringolaringee. *Rassegna internaz. clin. e terap.*, *13*:1135, 1932.

23. BINDER, A.: Ein primares sarkom des herzens. *Verhandl. deutsch. path. Gesellsch.*, *16*:417, 1913.

24. BITNER, A.I.: Idiopathic multiple hemorrhagic sarcoma of Kaposi. *A.M.A. Arch. Dermat.*, *72*:384 (Oct.) 1955.

25a. BLOOM, D.: In discussion on Andrews (6b).

b. BLOOM, D.: In discussion on Costello (48a).

26a. BLUEFARB, S.M.: Multiple idiopathic hemorrhagic sarcoma. Case presented at the Chicago Dermatological Society meeting (Oct.) 1955.

b. BLUEFARB, S.M. AND ROOT, H.H.: Oral manifestations of the

blood diseases. Eye, Ear, Nose & Throat Monthly, 31:309, 1952.

c. Bluefarb, S.M., and Webster, J.R.: Kaposi's sarcoma associated with lymphosarcoma. A.M.A. Arch. Int. Med., 91:97 (Jan.) 1953.

27. Blumenthal, F. and Staff: Kaposi's hemorrhagic sarcoma and hidradenitis suppurativa. *Arch. Dermat. & Syph.*, 62:938 (Dec.) 1950.

28. Braun, G. and Selffer, E.: Sarcoma idiopathicum multiplex hemorrhagicum (Kaposi). *Arch. f. Dermat. u. Syph.*, 141:88, 18....

29. Brayton, A.W.: Presentation of rare cases of skin diseases (Kaposi's disease). 19th annual meeting of the Mississippi Valley Medical Association, Abstracts of the papers and discussions. *J. Indiana M.A.*, 12:153 (Nov.) 1893.

30. Braunstein, H.A.: Multiple idiopathic hemorrhagic sarcoma of Kaposi. *Arch. Dermat. & Syph.*, 60:855 (Nov.) 1949.

31. Bunch, J.L.: Case of multiple idiopathic hemorrhagic sarcoma. *Proc. Roy. Soc. Med. (Sect. Dermat.)*, 14:10, 1920-21.

32. Buccellato, G.: Tumori d'emblée nel morbo di Kaposi. *Rassegna di dermat. e sif.*, 2:249 (May-June) 1949.

33. Burckhardt, W.: Morbus Kaposi. Dermatologica, 93:321, 1946.

34. Cajafa, E.: Alterazioni ossee nel morbo di Kaposi. *Atti XXXV Cong. Soc. Ital. Ortop. e Traumatol.*, (Oct.) 1951.

35. Cardoso, B. and Siccomi, P.: Sarcomatosi cutanea multipla emorragica di Kaposi. *Rinasc. Med.*, 11:365, 1934.

36. Case Report. Primary sarcoma (probably fibrosarcoma) of the right ankle, Case 22491 of the Massachusetts General Hospital. *New England J. Med.*, 215:1052 (Dec. 3) 1936.

37. Case Report: Sarcoma of Kaposi beginning at five years of age presented at Dermatological Conference, Mississippi Valley and Central States Dermatological Association. *Arch. Dermat. & Syph.*, 44:694 (Oct.) 1941.

38. Cattaneo, L.: Due casi di sarcoma Kaposi con localizzazioni esclusive ad un arto. *Boll. sez. region. Soc. ital. dermat.* No. 1, p. 84 (Apr.) 1933.

39a. Chargin, L.: Idiopathic multiple hemorrhagic sarcoma of Kaposi, Arch. Dermat. & Syph., 8:97 (July) 1923.

b. Chargin, L.: In discussion on Silvers (237a).

40. Choisser, R.M. and Ramsey, E.M.: *Angioreticuloendothelioma* (Kaposi's disease) of the heart. *Am. J. Path.*, 15:155 (Mar.) 1939.

41. Civatte, A.: In discussion on Jeanselme, *et al.* (126).

42. CLERC, A. AND OTHERS Un cas de tumeurs myxoïde siegeant dans l'oreillette droite. *Arch. d. mal. du coeur* 30:361 (June) 1937

43. COBURN J G AND MORGAN J.K.: Multiple idiopathic hemorrhagic sarcoma of Kaposi. *A.M.A. Arch. Dermat.*, 71 618 (May) 1955

44. COLE, H N AND CRUMP E.S. Report of two cases of idiopathic hemorrhagic sarcoma (Kaposi) the first complicated with lymphatic leukemia. *Arch. Dermat. & Syph* 1.283 (Mar) 1920

45. COMEL, M Sarcoma di Kaposi con diffusione all'albero respiratorio con reperto broncoscopico. *Gior ital. dermat e sif* 75 206 1934

46. CORNBLEET T Kaposi's sarcoma. *Arch. Dermat. & Syph* 38.827 (Nov) 1938

47. CORSON, E F AND KNOWLES, F C. Kaposi's sarcoma. *Arch. Dermat. & Syph* 46.293 (Aug.) 1942

48a CONTELLO, M J Kaposi sarcoma and leukonychia. *Arch. Dermat & Syph* 41 618 (Mar) 1940

b COSTELLO M J Kaposi sarcoma *Ibid* 60.973 (Nov) 1949.

49 CROCKER, H R Cited by Gilchrist and Ketron (87b)

50 CUNHA MOTTA, L. Hemangio reticulo-endotelioma. *An Fac med Univ Sao Paulo*, 1 627 1941

51 CUILLERAT P AND GALLET J Angiosarcome de Kaposi a debut *Bull. Soc franc de dermat et syph* 5 103 (Apr 19) 1945.

52 DALLA FAVERA, G.B Ueber das sogenannten sarcoma idiopathicum multiplex haemorrhagicum (Kaposi) klinische und histologische beitrage *Arch. Dermat u. Syph.*, 109 387 1911

53. DE AMICIS, T Die sarkomatose der haut. *Monatschr prakt Dermat* 25 309 (Oct) 1897

54. DENZER, B S AND LEOPOLD, H C Idiopathic hemorrhagic sarcoma (Kaposi) *Am J Dis Child* 52 1139 (Nov) 1936.

55. DILLARD C J AND WEIDMAN F D Multiple hemorrhagic sarcoma of Kaposi. *Histologic studies of two cases, one disclosing intestinal lesions at necropsy* *Arch. Dermat & Syph* 11 203 (Feb) 1925

56 DORFFEL, J Histogenesis of multiple idiopathic hemorrhagic sarcoma of Kaposi. *Arch Dermat & Syph* 26 608 (Oct) 193_

57 DOWNING J G Kaposi sarcoma *Arch Dermat & Syph* 45 152 (Feb) 1942

58a DUPONT A Note sur la maladie de Kaposi. *Bull assoc franc etude cancer* _3 46 1934

b. Dupont, A.: A propos des modifications de la formule sanguine dans l'angioreticulose de Kaposi. *Arch. belges dermat. et syph.*, *6*:206, 1950.

59. Ebert, M.H. and Otsuka, M.: Kaposi's sarcoma associated with a malignant tumor of the colon. *Arch. Dermat. & Syph.*, *50*:61 (July) 1944.

60. Ehrenberg, L.: Zwei falle von tumor im herzen. *Arch. Klin. Med.*, *103*:293, 1911.

61. Ehrmann, O.S.: Die behandlung des sarkom idiopathicum haemorrhagicum (tanturri fuleschich pigmentosum Kaposi) mit Quarzlicht. *Wien. med. Wchnschr.* *63*:2336 (Sept. 13) 1913.

62. Eljasz, A. Uber einen fall von Kaposi-sarkom mit hauthornartiger bildung und blasentumor. *Arch. Dermat. u. Syph.*, *164*:650, 1931.

63. Ellis, J.J. and Kent, L.H.: Kaposi's sarcoma of the legs and lupus vulgaris of the nose in the same patient. Presented at the Atlantic City Dermat. Conf., New York City (Mar. 9) 1940.

64. Ellis, F.A. Multiple idiopathic hemorrhagic sarcoma of Kaposi. Report of a case in an American Negro. *Arch. Dermat. & Syph.*, *30*:706 (Nov.) 1934.

65. Epstein, E. A case for diagnosis (Kaposi's sarcoma?) A.M.A. *Arch. Dermat. & Syph.* *43*:409, 1941.

66. Ess, L. Cited by Greenstein and Conston (96)

67. Eaton, M.M. Kaposi's sarcoma. *Arch. Dermat. & Syph.* *48*:665 (Dec.) 1943.

68a. Ewing, J. Cited by Fraser (81b)

b. Ewing, J. *Neoplastic Diseases*, Ed. 4. Philadelphia, Saunders, 1940.

69. Fabler, E.M. Schmidt, O.E.L. and Weber, W.E. Kaposi's sarcoma simulating stasis ulcers of the legs. *Stanford M. Bull.*, *7*:78 (May) 1949.

70. Fett, H.L. Sarcoma (Kaposi) *Arch. Dermat. & Syph.*, *18*:611 (Oct.) 1928.

71. Feldman, S. Sarcoma Kaposi? *Arch. Dermat. & Syph.*, *27*:602 (Apr.) 1933 and *28*:112 (July) 1933.

b. Feldman, S. Kaposi' sarcoma *Ibid.* *30*:482 (Sept.) 1934.

72. Findlay, C.M. Kaposi's multiple idiopathic hemorrhagic sarcoma. *Tr. Roy. Soc. Trop. Med. & Hyg.*, *40*:331 (Dec.) 1946.

73a. Fineberg, C.W. Kaposi's sarcoma. *Arch. Dermat. & Syph.* *12*:583 (Oct.) 1925.

b. Fineberg, C.W. In discussion on Schuller et al. (219)

74. FISCHER, J.W. AND COHEN D.M.: Simultaneous occurrence of kaposi's sarcoma, leukemia and diabetes mellitus. *Am. J. Clin. Path.*, *21*:586 (June) 1951.
75. FISCHER-WASELS, B.: Metaplasie und Geschwulstbildung, in: Bethe A. and Others *Handbuch der normalen und pathologischen Physiologie mit Berucksichtigung der experimentellen Pharmakologie.* Berlin, Springer 1927 vol. 14, pt. 2, p. 1211
76. FISCHL, F. Sarcoma idiopathicum multiplex haemorragicum. *Arch. Dermat. u. Syph.*, *119*:19, 1915- *Ibid.*, *137*:107 1921
77. FLARER, F. Cited by Bertaccini (21c)
78. FORDYCE, J.A. Endothelioma of the skin developing in the scar tissue of lupus vulgaris; angiosarcoma of the skin. *Am. J. M. Sc. 120*:159 1900
79a. FORMAN L. Kaposi's disease. *Brit. J. Dermat. 47*:172, 1935
b. FORMAN L. Kaposi's sarcoma. *Ibid.*, *48*:151 1936.
c. FORMAN L. Kaposi's idiopathic multiple pigment sarcoma. *Ibid. 51*:366, 1939
80a. FOX, H. In discussion on Wise (285c)
b. FOX, H. In discussion on Wise F. Kaposi sarcoma. *Arch. Dermat. & Syph. 7*:838 (June) 1923.
81a. FRASER, J.F. In discussion on Traub (200)
b. FRASER, J.F. Kaposi's sarcoma. *Arch. Dermat. & Syph.*, *28*:143 (July) 1933
c. FRASER, J.F. In discussion on Rubson (216)
82. FROLICH, H.J. Zur Lasuistik und therapie (Antileprol) des morbus Kaposi. *Dermat. Wchnschr. 104*:633, 1937
83. FROST, K.P. A case of multiple idiopathic hemorrhagic sarcoma (Kaposi) *Arch. Dermat. & Syph.* 3:155 (Feb.) 1921
84. FUNK, I. Clinical studies on sarcomata of the skin. *Brit. J. Dermat.*, *1*:143 (Mar.) 1889.
85. GANS, O. Histologie der Hautkrankheiten die Gewebsveränderungen, in *Der Kranken Haut unter Berucksichtigung ihrer Entstehung und ihres Ablaufs.* Berlin, Springer 1928, vol. — p. 462
86. GARBER, V.C. Kaposi' sarcoma in a Negro. *Arch. Dermat. & Syph. 38*:935 (Dec.) 1938.
87a. GILCHRIST T.C. In discussion on Wise, F. Kaposi's sarcoma. *Arch. Dermat. & Syph.* 8:143 (July) 1933.
b. GILCHRIST T.C. AND KETRON L.W. Report of two cases of idiopathic hemorrhagic sarcoma (Kaposi) one presenting unusual features with special methods of treatment and investigation. *J. Cutan. Dis.* 34:429 (June) 1916

88. GILLET M.: A case of Kaposi's angiosarcoma. *Cahiers medicaux de l'union francaise*, 4:441, 1949. *Abst.: Excerpta Med.*, 5:95, 1951.

89. GOLDSMITH, W.N.: The reticuloses. *Brit. J. Dermat.*, 56:107 1944.

90. GOLDSCHLAG, F. Ueber einen fall von sarcoma idiopathicum haemorrhagicum Kaposi mit ungewohnlichem verstadium. *Dermat. Wchnschr.*, 100:204 (Feb.) 1935.

91. GONZALES, H.D. AND VIDAURRETA, M.F.: Sarcomatosis de Kaposi. *Prensa med. argent.*, 19:366, 1932.

92a. GOUGEROT H. AND BURNIER, R.: Maladie de Kaposi uniquement palmaire. *Bull. Soc. franc. dermat. et syph.*, 45:387 (Mar.) 1938.

b. GOUGEROT H., BURNIER, R. AND ELIASCHEFF O. Forme pigmentaire et hemorrhagique de sarcomatose de Kaposi. *Ibid.*, 40:1609, 1933.

c. GOUGEROT H. PETIT, A. AND PETRAUDI Acrosarcomatose de Kaposi polymorphe et bulleuse: forme atypique. *Ibid.*, 44:640, 1937

93. GRAHAM, T.N. Idiopathic multiple hemorrhagic sarcoma (Kaposi) report of unusual case in which the initial lesion was on the eyelid. *Arch. Ophth.*, 27:1188 (June) 1942.

94. GRAHAM-LITTLE, E.G. Multiple idiopathic hemorrhagic sarcoma of Kaposi. *Brit. J. Dermat.*, 30:213, 1918.

95. GRECO, N.V. Elementos clinico-etiologicos de un caso de enfermedad (sarcomatosis) de Kaposi. *Semana méd.*, 2:1 61 (Dec. 24) 1936

96. GREENSTEIN, R.H. AND COMPTON, A.S. Co-existent Hodgkin's disease and Kaposi's sarcoma. *Am. J. M. Sc.* 218:384 (Oct.) 1949.

97. GRIFFI, E. AND BETTONI, I. Splenomegalia emolitica ed angioendotelioma cutaneo tipo Kaposi con associazione di agranulocitosi e sepsi orale. Sindrome complessa di eticoloendoteliosi hiperplastico-neoplastica. *Arch. Ist Biochim. ital.* 4:403, 1932.

98. GRIGORJEW P.S. Zur kenntnis des multiplen idiopathischen hemorrhagischen sarkoms (Kaposi). *Arch. Dermat. u. Syph.*, 146:384 19 4.

99. GRILLO, V. Su di un voluminoso fibromixoma dell'endocardio. *Pathologica* 4:405, 1932.

100. GRINSPAN D. "Sarcomatosis de Kaposi. Buenos Aires, Libreria y Editorial "El Ateneo, 1950

101a. GROSS, P. Multiple idiopathic hemorrhagic sarcoma (Kaposi) with lesions in the mouth. *Arch. Dermat. & Syph.*, 30:153 (July) 1934

b. Gross, P Kaposi sarcoma with low grade spindle cell sarcoma. *Ibid.*, 43 428 (Feb.) 1941
102. Grzybowski, M. Contribution a l'etude de l'histogenese de la maladie de Kaposi. *Ann. de Dermat. et syph.*, 5:135, 1934.
103. Guarini, C.: La cura del sarcoma idiopatico del Kaposi con la roentgenterapia. *Arch. radiol.*, 2,40, 1926.
104. Guccione, F Contributo allo studio patogenetico della malattia di Kaposi. *Arch. ital. di anat. e istol. pat.*, 5,1 1934
105. Halle, A.: Ein beitrag zur kenntnis des sarcoma idiopathicum multiplex haemorrhagicum (Kaposi) *Arch. Dermat. u. Syph.*, 72 373, 1904.
106. Hamdi, H and Rebat H. Sur l'histologie de la sarcomatose de Kaposi (acroperithelioma idiopathicum multiplex cavernosum lymphangiectodes cutaneum) *Ann d'anat. path.*, 9 593, 1932.
107 Hamilton Paterson J L. and Castleden L I.M Intracardiac tumors *Brit Heart J* 4 103, 1942.
108. Hansson, C J Kaposi's sarcoma clinical and radiotherapeutic studies on twenty-three patients. *Acta radiol* 21 457 (Oct) 1940
109a. Hardaway W.A Case of pigmented neoplasm of the skin. *J Cutan & Vener Dis* 1 97 (Jan) 1883
b Hardaway W A Spontaneous involution of sarcoma. *J Cutan & G U Dis* 8 21 (Jan) 1890
110 Harf H F Frommer, J L., Trump J G Wright A and Anson J H. Cathode ray treatment for lymphomas involving skin. *A M.A Arch Dermat* 68 635 (Dec) 1953
111 Hartzell, M B Idiopathic multiple hemorrhagic sarcoma (Kaposi) *J Cutan Dis* 26 97 (Mar) 1908
112 Ha s, A Ein fall von sarcoma idiopathicum multiplex cutis pigment. *Abstr Arch Dermat u. Syph* 30:283, 1888.
113. Hazen H.H. Mycosis fungoides and similar conditions in the Negro *Arch Dermat & Syph* 55 111 (Jan) 1947
114. Hecht, H M Sarcoma (Kaposi) *Arch Dermat & Syph* 16 91 (July) 1927
115. Heimann F Sarcoma haemorrhagicum multiplex idiopathicum of Kaposi *J Cutan Dis* 31 1.4 1913
116 Herzog, G Uber die bedeutung der gefasswandzellen in der pathologie *Klin Wchnschr* 2 684 (Apr 9) and 730 (Apr 16) 1923.
117 Hewer, T F nd Kemp R P Malignant hemangio-endothelioma of the heart report of case *J Path & Bact* 43 511 1936
118 Higgi C K Kaposi tumor *Brooklyn Hosp. J* 9 167 1951

119a. Hirschman, W. J.: Kaposi's sarcoma lasting for 23 years. *Arch. Dermat. & Syph., 18*:987 (Dec.) 1928.

b. Hirschman, W. J.: In discussion on Fraser (81b)

120. Hogeman, O.: Hyperhemolysis of non-splenic origin. *Acta med. scandinav., 144*:247 1953.

121. Hohlbaum, H.: Zur histologie der Kaposischen krankheit. *Centralbl. f. allg. Path. u. path. Anat., 63*:241, 1935.

122a. Hudelo, L. and Cailliau, F.: La sarcomatose idiopathique pigmentaire multiple de Kaposi et ses interpretations histogenetiques et pathogeniques. *Ann. dermat. et syph., 2*:417 (Apr.) 1931.

b. Hudelo, L., Cailliau, F. and Chenaki: Pseudo-sarcomatose telangiectasique de Kaposi. *Bull. Soc. franc. dermat. et syph., 35*:380, 1928.

123. Hufnagel, L. and Dupont, A.: Sarcomatose idiopathique de Kaposi et leucemie lymphoide. *Bull. Soc. franc. de dermat. et syph.* 38:058, 1931.

124. Hurlbut, W.B. and Lincoln, Jr., C.S.: Multiple hemorrhagic sarcoma and diabetes mellitus. *Arch. Int. Med., 84*:738 (Nov.) 1949.

125. J comsson, A.: Sarcoma idiopathicum haemorrhagicum (Kaposi). Nord. med., 12:3085 (Nov. 1) 1941.

126. Jeanselme, E. and Others: A propos d'un cas de sarcomatose de Kaposi: etude anatomoclinique et essai d'inoculation aux gallinaces. *Bull. Soc. franc. de Dermat. et Syph.* 35:384 (May) 1928.

127. Jansen, D.S.D.: Kaposi's sarcoma. *Am. J. Cancer* 31:556 (Dec.) 1937.

128. Jojot, C. and Laigret, J.: Un cas de tumeurs superficielles observed au Cameroun. *Bull. Soc. path. exot.* 18:856, 1925.

129. Jordan, A.: Sarcoma idiopathicum multiplex haemorrhagicum (Demonstration of a case presented at the Venereologisch-dermatologische Gesellschaft zu Moskau.) *Monatschr. f. prakt. Dermat.* 32:343, 1901.

130. J[illegible], J.: Uber Ubertragung von sarcoma idiopathicum haemorrhagicum Kaposi auf tiere. *Arch. Dermat. u. Syph.* 99:116, 1910 and Sarcoma idiopathicum Kaposi, *Ibid., 151*:436, 1926.

131. Kamdar, B. and Murray, J.F.: Sarcoma idiopathicum multiplex haemorrhagicum of Kaposi, with special reference to it incidence in the South African Negro, and two case reports. *South African J. M. Sc.* 1:1 (Mar.) 1950.

132a. Kaposi, M.: Idiopathisches multiples pigment-sarkom der haut. *Arch. Dermat. u. Syph.* 4:265, 1872.

b. Kaposi, M: Zur nomenclatur des idiopathischen pigmentsarcoms Kaposi. *Ibid* 29:164, 1894.

c. Kaposi, M Sarcoma multiplex pigmentosum. *Ibid.*, 49.133, 1899.

133 Kessel, L: A case of Kaposi's haemangiosarcoma. *Arch. Dis. Childhood* 27 153 (Apr) 1952.

134a. Kingsbury J Multiple hemorrhagic sarcoma. *J Cutan. Dis.*, 31.575 (Aug.) 1913.

b. Kingsbury J In discussion on Lane (144)

135a. Klaber, R. Case for diagnosis acrodermatitis chronica atrophicans? (later proved to be Kaposi's idiopathic hemorrhagic sarcoma) *Brit J Dermat.*, 46.38, 1934.

b Klaber, R. Kaposi's disease. *Ibid* 50:377 1938.

Klaber, R Kaposi's disease. *Proc Roy Soc. Med (Sect Dermat)* 36.616 (May 20) 1943.

136 Kocsard, E. Kaposi sarcoma in a Chinese boy (aged 16 years) with localization on the left lower extremity and on the right caruncula lacrimalis. *Dermatologica* 89 43, 1910

137 Koebner, H Zur kenntnis der allgemeinen sarcomatose und der hautsarcoma im besonderen. *Arch f Dermat u Syph* 1 369 1869 and Vorstellung eines falles on multiplen hautsarkomen der extremitaten. *Berl Klin. Wchnschr* 23.193 1886

b Koebner, H Krankenvorstellung (idiopathisches multiples sarcoma haemorrhagicum der extremitaten) *Arch Dermat u. Syph* 23 119, 1891

138 Kreibich, C Ueber granulome *Arch Dermat u Syph.*, 94 1.1 1909

139 Kren O Sarcoma Idiopathicum Hemorrhagicum (Kaposi) in Jadassohn J *Handbuch der Haut und Geschlechtskrankheiten* Berlin, J Springer 1933 ol. 12, pt. 3, p. 841

140. Krestnikow D P Zur frage des multiplen idiopathischen haemorrhagischen sarcoms Kaposi. *Zentralbl Haut. u Gesch* 9 117 1923

141 Kutchar, C V Benign and malignant tumors of the foot *J A M A.*, 1.4 761 (Mar 18) 1944

142. Kusnetzow W N A case of sarcoma multiplex idiopathicum (Kaposi) with fatal outcome. *Urol & Cutan Rev* 37 230 (Apr) 1933.

143. Lane, C G and Greenwood, A M Lymphoblastoma (mycosis fungoides) and hemorrhagic sarcoma of Kaposi in the same person *Arch Dermat & Syph.*, 27 643 (Apr) 1933

144. Lane, J E Kaposi sarcoma *Arch Dermat & Syph* 26.733, 1932.

145. LANG, F J AND HAELBOWER, L.: Ueber die auffassung der Kaposischen krankheit als systematisierte angiomatose. *Ztschr. Krebsforsch*, 42:63, 1935.

146. LAPOWSKI, B: Idiopathic multiple pigment sarcoma (Kaposi) *Arch. Dermat. & Syph.*, 33:170 (Jan.) 1936.

147. LIEBERMANN, R.: Multiplen idiopathischen haemorrhagischen hautsarkom. *Arch. Dermat. u. Syph.*, 70:144, 1904.

148. LIGORIO, V: Considerazioni sopra un caso di sarcoma idiopatico fi Kaposi (angioendotelioma cutaneo di Kaposi) di non commune inizio ed evoluzione. *Arch. ital. dermat.* ... 11:461 1935.

149. LIEBERMANN, W.: In discussion on Skoblo (241)

150. LEVER, W.F *Histopathology of the Skin.* Philadelphia, Lippincott, 1949 p. 375.

151a. LIEBERTHAL, D.: Sarcomatosis cutis. *J.A.M.A.*, 39:1454 (Dec. 6) 1902.

b. LIEBERTHAL, D: Idiopathic multiple hemorrhagic sarcoma (Kaposi) Trauma an etiological factor (?) *J Cutan. Dis.*, 27:522 (Nov) 1909.

152. LOWENTHAL, L.J.A. Multiple idiopathic hemorrhagic sarcoma of Kaposi (report of a fourth case in a full-blooded Negro) *Arch. Dermat. & Syph.*, 37:972 (June) 1938.

153. MCCARTHY W.D AND PACK, G.T Malignant blood vessel tumors. *Surg., Gynec. & Obst.*, 91 465 (Oct.) 1950.

154. MCGINN, J T RICCA, J J AND CURRIN, J F Kaposi's sarcoma following allergic angiitis. *Ann. Int. Med.*, 42:921 (Apr) 1955.

155a. MACKEE, G M *X Rays and Radium in the Treatment of Diseases of the Skin.* Ed. 2, Philadelphia, Lea, 1927 p 707

b. MACKEE, G M. AND CIPOLLARO, A.C.: Idiopathic multiple hemorrhagic sarcoma (Kaposi) *Am. J Cancer* 26:1 1936.

156. MACKENZIE, S: Remarks on various diseases of the skin. *Brit. M J* 1 4 (Jan 4) 1890

157. MCLEAN, S. A case of idiopathic hemorrhagic sarcoma of Kaposi. *Am. J Dis. Child.*, 21 437 (May) 1921

158. MACLEOD, J M H. Notes on the histopathology of multiple idiopathic hemorrhagic sarcoma *Brit. J Dermat.*, 17 173 (May) 1905.

159. MARCHAND, F Cited by Hertog (116)

160. MARIANI, G Sarkomatosis Kaposi mit besonderer berucksichtungung der visceralen lokalisationen. *Arch. f Dermat. u. Syph* 98:267 1909 and Ueber das sarkoma idiopathicum Kaposi. *Ibid* 97 334, 1909

161. Martensson J and Henrickson H. Immuno-hemolytic anemia in Kaposi's sarcoma with visceral involvement only. *Acta med. scandinav.*, 150-3, 1954.
162. Masson, M.P.: In discussion of Ramel (203)
163. Masson, P. Les naevi pigmentaires, tumeurs nerveuses. *Ann. d'anat. Path.*, 3 417 (May) 1926 and 3 657 (July) 1926.
164a. Maximow A.A. Cited by Dorffel (56)
b. Maximow A.A. and Bloom, W. A *Textbook of Histology* Ed. 3. Philadelphia, Saunders, 1938, p. 93.
165. Mendes da Costa, S.: Ein fall von Kaposi's pigmentsarkom, Festschrift fur Unna, No. 1 *Dermat. Stud.*, 20:212, 1910.
166. Metscherski, G.I. Sarcoma melanopigmentosum multiplex cutis. *Monatschr. f. prakt. Dermat.* 30 516, 1900.
167. Meyers, D.S. and Jacobson, V.C. Multiple hemorrhagic sarcoma of Kaposi. *Am. J. Path.*, 3.3..1 (July) 1927
168. Michelson, H.E. In discussion on Mitchell, J.H. Mycosis fungoides treated with sodium paraaminobenzoic acid. *Arch. Dermat. & Syph.* 60 885 (Nov.) 1949
169. Mierzecki, H. Sarcoma idiopathicum multiplex Kaposi. *Arch. Dermat. u. Syph.* 165.577 1932.
170. Miller, H.E. In discussion on Mitchell (171)
171. Mitchell, D.S. Kaposi' sarcoma *Arch. Dermat. & Syph.* 41 404 (Feb.) 1940.
172. Mitchell, N. and Feder, I.A. Kaposi' sarcoma with secondary involvement of the jejunum, perforation and peritonitis. *Ann. Int. Med.*, 31 324 (Aug.) 1949.
173. Morrow H. In discussion on Torrey (238)
174. Morse, J.L. Kaposi's sarcoma. *Arch. Dermat. & Syph.*, 47 603 (Apr.) 1943.
175. Muller, W. Uber polypose bosartige, metastasierende endokardgewachse und gewachs-artige thromben der linken herzvorhofs. *Virchows Arch. path. Anat.* 284 105, 193..
176. Nesbitt S., Mark, P.F. and Zimmerman, H.M. Disseminated visceral idiopathic hemorrhagic sarcoma (Kaposi's disease); report of a case with necropsy findings. *Ann. Int. Med.* 22 601 (Apr.) 1945.
177. Newman, B.A. Multiple idiopathic hemorrhagic sarcoma (Kaposi) producing urethral stricture. *Arch. Dermat. & Syph.*, 47 293 (Feb.) 1943
178. Nicolas J and Favre, M. A propos de l'interpretation de l'affection dite sarcomatose t langiectasique pigmentaire de Kaposi. *Bull. Soc. franc. de dermat. et syph.* 35 15.., 1928.
179. Nuss, H.D. Kaposi' hemorrhagic sarcoma. *Arch. Dermat. & Syph.* 33.913 (May) 1936.

180. Nödl, F.: Zur histogenese der angiomatosis Kaposi. *Dermat. Wchnschr* 121:247 1950.

181. Norris, W.H.: Myxoma of the heart simulating bronchopneumonia. *Am. J. M. Sc.*, 158:680 (Nov.) 1919.

182. Noto P. Malattia di Kaposi ed alterazioni oculari. *Gior. ital. di Oftal.*, 3:204, (May-June) 1950.

183. Ochs, B.F.: Sarcoma (Kaposi) *Arch. Dermat. & Syph.*, 18:630 (Oct.) 1928.

184. O'Leary P.A.: In discussion on Senear and Wien (232 b)

185. Oppenheim, M. Idiopathic multiple pigmented sarcoma (Kaposi?) *Arch. Dermat. & Syph.*, 54:435 (Aug.) 1946.

186a. Ormsby O.S. and Mitchell, J.H. Idiopathic multiple hemorrhagic sarcoma. *Arch. Dermat. & Syph* 3:447 (Apr.) 1921

b. Ormsby O.S. and Montgomery H. *Diseases of the Skin*, Ed. 6. Philadelphia, Lea, 1943.

187 Osborne, E.A., Jordan J.W. Hoak, F.C. and Pschierer, F.J.: Nitrogen mustard therapy in cutaneous blastomatous diseases. J.A.M.A. 135:1123 (Dec. 27) 1947

188a. Pack, G.T. Idiopathic multiple hemorrhagic sarcoma of Kaposi. *J. M. Soc. New Jersey* 34:603 (Oct.) 1937

b. Pack, G.T. *Tumors of the Hands and Feet.* St. Louis, Mosby 1939 p. 10

189 Paolini, R. Sul sarcoma moltepilce primitivo di Kaposi con speciale riguardo alle localizzazioni viscerali. Studio clinico anatomo-isto-patologico batteriologico. *Zentralbl. f. Haut. u. Geschl.*, 26:816, 1928.

190. Pardo-Castello, V. Sarcoma hemorrhagico de Kaposi, relacion de un caso en un individuo de la raza de color *Bol. Soc. cubana de dermat.*, 2:100 1931

191a Pautrier, L.M. and Diss, A. Sur les lesions vasculo-nerveuse de la pseudosarcomatose de Kaposi *Bull. Soc. franç. de dermat. et syph.* 35:145 1928

b Pautrier, L.M. and Diss, A. Kaposi sarcoma is not a genuine sarcoma but a neurovascular dysgenesis. *Brit. J. Dermat.*, 41:93 (Mar.) 1929

Pautrier, L.M. a[illegible] [illegible] A. Angiomatose Kaposi of the buccal mucous membrane and tongue, simulating a carcinoma, and treated satisf[illegible] with x-ray therapy Dermatologica, 9[illegible]:44, 1946

192 Pearcy, C.T. and Va[illegible] L.E. Multiple hemorrhagic sarcoma of the skin (Kaposi) *Ohio State M.J.* 32:137 (Feb.) 1936

193 Pr[illegible] S.M. In discussion on Wolf (257)

194. PELAGATTI, M.: Die hautsarkomatose. *Monatsh. f prakt. Dermat.*, 35:249 (Sept.) 1902 and Ueber das sarcoma multiplex Kaposi. *Arch. Dermat. u. Syph.*, 83:278, 1907

195a. PERRIN L. *De la Sarcomatose Cutanee.* Paris, G. Steinheil, 1886.
b. PERRIN L. Sarcomes, In *La Pratique Dermatologique.* Paris, Masson 1904, vol. 4, p. 204.

196. PERRY B.P AND LIRA, J.R.: Multiple idiopathic hemorrhagic sarcoma of Kaposi in a full-blooded Negro. *Arch. Dermat & Syph.*, 49 270 (Apr) 1944.

197. PHILIPPSON L. Ueber das sarcoma idiopathicum cutis Kaposi: ein beitrag zur sarcomlehre. *Virchows Arch. f path. Anat.*, 167 58, 1902.

198a. PICK, W Zur kenntnis des kaposi schen pigmentsarkoms. *Arch. Dermat. u. Syph.*, 87:267 1907
b. PICK, W : Zur kenntnis des senilen angioms und seiner beziehungen zum endothelium. *Ibid* 99-109 1910

199a. POLLITZER, S. Cited by Pautrier and Diss (191b)
b. POLLITZER, S. In discussion on Wolf (287)

200. PROKOPCUK, A. AND CUTALOVA, M. Zur frage des multiplen idiopathischen haemorrhagischen sarkoms Kaposi. *Zentralbl. Haut. u. Gesch.*, 28:171 1929

201. PUHR, L. Beitrag zur kenntnis der hautsarkoide. *Dermat. Wchnschr.*, 91 1815, 1930 and Ueber das idiopathische multiple pigmentsarkom der haut (Kaposi) *Arch. f Dermat u. Syph.*, 164:167 1931

202. RADAELI F Contributo alla conoscenza del sarcoma multiplo idiopatico emorragico del cute *Gior ital mal vener e d. pelle* 43 536, 1902, abstr *ibid* 46 27, 1905, and Sul proceso anatomo-patologico del sarcoma idiopatico di Kaposi (angio-endotelioma cutaneo di Kaposi) *Gior ital dermat. e sif* 71 1501 1930

203. RAMEL, E. Sarcomatose idiopathique hemorrhagique (Kaposi) *Bull Soc franc de Dermat et Syph* 33 557 1926

204. RATTNER, H. AND SCHAUDER, I Kaposi sarcoma. *Arch Dermat & Syph* 42.514 (Sept.) 1940

205. RAVAUT P AND CACHERA, R. A case of Kaposi's cutaneous sarcomatosis associated with an arteritis of the lower extremities and a purpuric syndrome. Abstr : *Am. J Cancer* 18:1317 193_

206. RAW N Primary tumor of right auricle of heart, rupture of inferior vena cava *Brit M J* 2.1353 (Oct 29) 1898

207. RIEHL, C Sarcomatosi cutis idiopathica *Arch Dermat u Syph.*, 70 134, 1904, and Ein rhinosklerom und einen fall von hamorrhagischen hautsarkom *Ibid.*, 74 81 1905

208. Bocca, H. and Vigne, P.: Compression médullaire et ostéite fibro-kystique de Recklinghausen au cours d'une sarcomatose de Kaposi. Rev. neurol., 65:1467 1936.

209. Bogowsky M.: Kaposi's angiomatosis in a Negro of Belgian Congo. *Arch. belges Dermat. et Syph.*, 6:18 (Mar.) 1950

210a. Ronchese, F and Kern, A.B.: Kaposi's sarcoma (angioreticulomatosis) *Postgrad. M* 14:101 (Aug.) 1953.

b. Ronchese, F and Kern A.B.: Bone lesions in Kaposi's sarcoma. A.M.A. Arch. Dermat., 70:342 (Sept.) 1954.

c. Ronchese, F and Kern, A.B. Lymphangioma-like tumors in Kaposi's sarcoma, Paper read at meeting of Am. Dermat. A., Santa Barbara, Calif., June 1956, to be published in A.M.A. *Arch. Dermat*

211. Rossle, R.: Ueber das gittermaschengerust der leber unter normalen und pathologischen bedingungen *Gesellsch. Morph. u. Physiol. in Munchen. Sitzungsberichte* 34:17 1908.

212. Rottenberg, A. A case for diagnosis (Kaposi's sarcoma?) Arch. *Dermat. & Syph.* 24:669 (Oct.) 1931

213. Rothman S and Hershberger, A.B Kaposi's sarcoma. Arch. *Dermat. & Syph.*, 48:466 (Oct.) 1943.

214. Rottman H.G Zur Kenntnis des sarcoma idiopathicum multiplex haemorrhagicum (Kaposi) Arch *Dermat u. Syph.*, 154 134 (Dec.) 1927

215. Rothschild, A.C. and Klaber, R. Kaposi's disease. *Brit. J Dermat.*, 50:375, 1938.

216. Robson R.H Multiple idiopathic sarcoma (Kaposi) *Arch Dermat & Syph* 38:102 (July) 1938.

217. Sachs, W Aurlay R.D and Cohen J Multiple idiopathic hemorrhagic sarcoma of Kaposi J Invest Dermat., 8:317 (June) 1947

b. Sachs, W and Gray M Kaposi sarcoma and lymphatic leukemia, report of a case with histological evidence of the two diseases in the same lesion. *Arch. Dermat & Syph* 51:3..5 (May) 1945

218. Santoro, G. Contributo allo studio del sarcoma idiopathicum multiplum haemorrhagicum Kaposi *Gior ital dermat e sif* 3:782, 1933

219. Saphier, J Zur kenntnis der sarcoma idiopathicum multiplex haemorrhagicum Kaposi Arch. *Dermat. u. Syph* 118:671 1913

220a. Satenstein, D.L. Cited by MacKee and Cipollaro (159b)

b. Satenstein, D.L. In discussion on Grow (101b)

221. Schirger, A.F. H... C.K. and Stadler, W.G. Kaposi's sarcoma Arch Dermat & Syph 38:315 (Aug.) 1938.

222. Schilling, V : *The Blood Picture and Its Clinical Significance.* St. Louis, Mosby 1929.

223. Schirotunskaja, K. and Tschotschia, K.: Ein fall von idiopathischem multiplem haemorrhagischem hautsarcom Kaposi und dessen Roentgenbehandlung. *Dermat. Wchnschr* 94:705, 1932.

224. Schirren, C.G. and Burkhardt L.: Ein sarcoma idiopathicum multiplex haemorrhagicum (Kaposi) mit hirnmetastasen. *Arch. klin. u. exper Dermatologie* 201:99, 1955.

225. Schmidt O.E.L.: Kaposi's sarcoma with involvement of the oropharynx and larynx. *Arch. Dermat & Syph.,* 45:438 (Feb. 1942.

226. Scholtz, W Multiples idiopathisches hautsarkom (Kaposi) *Arch. Dermat. u. Syph., 51*:309 (Nov) 1900.

227 Schwimmer, E L. Sarcoma idiopathicum multiplex cutis. *Abstr. Monatsschr prakt. Dermat* 9:90, 1889.

228 Seabrave, K.H. Kaposi's disease report of a case with unusual visceral manifestations. *Radiology 51*:248 (Aug.) 1948

229 Selhorst S.B. and Polano, M.E. Ein fall von sarcoma idiopathicum multiplex haemorrhagicum Kaposi. *Arch. Dermat. u. Syph., 82*:33, 1906

230. Sellei, J Weitere beitrage zur pathologie des sog. Sarcoma multiplex Pig. Haemorrh. Idiopathicum (Kaposi) *Arch. Dermat u Syph* 66:41 1903.

231 Semenow T V Zehn falle des sarcoma idiopathicum pigmentosum multiplex cutis. *Monatsschr prakt. Dermat* 25:539 1897

232a. Sinclair, F.E. and Caro, M.R Multiple idiopathic hemorrhagic sarcoma (Kaposi) *Arch. Dermat. & Syph* 38:277 (Aug) 1938.

b Sinclair, F.E. and Wien M S Multiple idiopathic hemorrhagic sarcoma (Kaposi) *Ibid* 27:851 (May) 1933

233a. Sequeira, J.H. Case of idiopathic multiple pigment sarcoma (?) *Brit J Dermat* 13:201 (June) 1901

b. Sequeira, J H Multiple idiopathic pigment sarcoma (so-called) of Kaposi, with report of an early case. *Ibid* 25:331 (Nov) 1913.

c. *Sequeira, J H. So-called multiple idiopathic pigment sarcoma* (Kaposi) *Ibid* 33:317 1921

d. Sequeira, J H and Bravo, R.T Development of true sarcoma in a case of multiple idiopathic pigment so-called sarcoma (Kaposi) *Ibid* 38:501 1926.

234. SERRA, G.: Contributo clinico ed istopatologico allo studio del cosidetto sarcoma cutaneo idiopatico multiplo emorragico di Kaposi. *Dermosifilografo* 6:553, 1931, *Abstr.: Am. J. Cancer* 16:1067 1932.

235. SHELBURNE, S.A. Primary tumors of the heart with special reference to certain features which led to a logical and correct diagnosis before death. *Ann. Int. Med.*, 9:340 (Sept.) 1935

236. SHERWIN, B. AND GOLDSMITH, H.: Kaposi's sarcoma. Case report with unique visceral manifestations. *Ann. Surg.*, 135:118 (Jan.) 1952.

237 SIBLEY W.K A case of so-called "Multiple Hemorrhagic Sarcoma (Kaposi) *Brit J Dermat* 32 331 (Nov) 1920.

238. SILVER, H. Kaposi's sarcoma with involvement of the eye. *Arch. Dermat. & Syph* 44 711 (Oct.) 1941.

239a. SILVER, S.H. Multiple idiopathic hemorrhagic sarcoma. *Arch. Dermat. & Syph.*, 44 626 (Sept.) 1941

b. SILVER, S.H. Kaposi's sarcoma of fifteen years duration. *Ibid.*, 48:665 (Dec.) 1943.

240. SKINNER, E F Notes on a case of multiple pigmented idiopathic sarcoma (Kaposi) *Brit J Dermat.*, 31:18 (Jan.) 1919

241. SLOMLO, M Multiple idiopathic haemorrhagic pigmented sarcoma (Kaposi) *Brit. J Dermat.*, 60:383 (Nov) 1948.

242. SMITH, D.S. Neoplastic involvement of the heart. *J.A M A.*, 109 1192 (Oct. 9) 1937

243. SMITH, H J AND SAMITZ, M.H. Multiple idiopathic hemorrhagic sarcoma of Kaposi. Arch Dermat & Syph 60 128 (July) 1949

244. SMITH, P Hemorrhagic sarcoma of Kaposi in a Negro. *A.M.A. Arch. Dermat* 72:594 (Dec) 1955.

245. SPOONER, G.J Multiple pigmented hemorrhagic sarcoma of Kaposi. Arch. Dermat. & Syph., 30-742 (Nov) 1934

246 STATS, D. Visceral manifestations of Kaposi sarcoma. *J Mt. Sinai Hosp* 12 971 (Jan. Feb.) 1946.

247 STEINER, V Pigmentsarkome der extremitaten. *Berl. Klin Wchnschr* 33.634, 1896.

248. STERNBERG, C. Ueber das sarcoma multiplex haemorrhagicum (Kaposi) *Arch Dermat u. Syph* 111 331 1912

249. STEWART F W AND TREVES, N Lymphangiosarcoma in post mastectomy lymphedema. *Cancer* 1:64 (May) 1948.

250. STILLIANS, A W AND SMITH, JR., E.M. Kaposi sarcoma with lesions of the face *Arch Dermat. & Syph* 41 596 (Mar) 1940.

251 STITCH, M.H., EIBER, H.B., MORRISON M. AND LOEWE, L.: Cytology of Kaposi's sarcoma. *Arch. Dermat. & Syph.* 67 85 (Jan.) 1953.

252. STRATTON, E.K. Multiple hemorrhagic sarcoma of Kaposi. *Urol. & Cutan. Rev.* 3...71 (Jan.) 1928.

253. SULZBERGER, M.B. Multiple idiopathic hemorrhagic sarcoma (Kaposi) *Arch. Dermat. & Syph.*, 36:455 (Aug.) 1937

254a. SYMMERS, D Kaposi's disease. *Arch. Path.*, 32: 64 (Nov.) 1941

b. SYMMERS, D: Personal communication to Pensky and Lisa (196)

255 SYNOP H.M AND KRANTZ, S Kaposi's disease; report of a case with unusual oropharyngeal manifestations occurring in a full-blooded Negro. *J Oral Surg.*, 4 337 1951

256. TALBOTT J.H Clinical manifestations of Hodgkin's disease. *New York State J.M.* 47 1853 (Sept. 1) 1947

257 TEDESCHI, C.G FOLSOM, H.F AND CARNICELLI, T.J Visceral Kaposi's disease *Arch. Path.* 43 335 (Apr.) 1947

258 TORREY F Idiopathic multiple hemorrhagic sarcoma (Kaposi) *Arch. Dermat. & Syph.* 25 734 (Apr.) 1932.

259 TRAMONTANO, V AND FITTIPALDI, C Contributo allo studio dell' ema gloendotelioma cutaneo del Kaposi ed alla coesistenza di differente blastomi *Arch. ital. dermat. sif.* 7 215, 1931

260 TRAU E F Sarcoma—Kaposi *Arch. Dermat. & Syph.* 1 260 (Feb.) 19...8.

261 TRIMBLE W In discussion on Wise (285e)

262. UHLMANN, E Beitrag zur frage des sarcoma idiopathicum multiplex haemorrhagicum Kaposi. *Arch. Dermat. u. Syph.* 150 120 1926

263. UNNA, P.G Histopathologie der Haut Krankheiten, in Orth, J Lehrbuch der Speciellen Pathologischen Anatomie. Berlin, A. Hirschwald, 1894 Ergänzungsband, part 2

264 U...GLIO G ZAMBELLI, E AND PAOLINO W Espressioni biochimiche sanguigne in un caso di morbo di Kaposi *Gior. Accad. med. Torino* 101 401 1938

265 VAN CLEVE, J.V AND HELLWIG C.A. Case of idiopathic hemorrhagic sarcoma (Kaposi) with autopsy findings *Urol. & Cutan. Rev.* 39 246 (Apr.) 1935.

266a. VIGNE, P Un nouveau cas de sarcomatose de Kaposi. *Bull. Soc. franç. de dermat. et syph.* 37 445 1930

b. VIGNE, P AND PEDAT Sarcomatose idiopathique de Kaposi *Ibid* 39 90 193..

267 VOGEL, W Fall on hochgradiger syphilischer phlebitis der ...na saphena magna *Arch. Dermat. u. Syph.* 1 3 383, 1920

268. Wallhauser, J.J.F.: Bichlorid of mercury in the treatment of idiopathic multiple hemorrhagic sarcoma. *J.A.M.A.*, 53:1608 (Nov. 13) 1909.

269a. Walker, A.: In discussion on Silvers (239a)

b. Walker, A. In discussion on Silvers (239b)

270. Warthin, A.S.: The genetic neoplastic relationships of Hodgkin's disease, aleukemic and leukemic lymphoblastoma, and mycosis fungoides. *Ann. Surg.*, 93:153 (Jan.) 1931.

271. Watson, W.L. and McCarthy, W.D. Blood and lymph vessel tumors. A report of 1,056 cases. *Surg., Gynec. & Obst.*, 71:569 (Nov.) 1940.

272. Way, S.C. and Klovekorn, G.H.: Hautkrankheiten und gitter fasern. *Dermat. Ztschr.* 48:139, 1926.

273a. Weber, F.P. Hemorrhagic telangiectasis of the Osler type—telangiectatic dysplasia. An isolated case, with discussion on multiple pulsating stellate telangiectases and other striking haemangiectatic conditions. *Brit. J. Dermat.*, 48:182 (Apr.) 1936.

b. Weber, F.P. and Daser, P. Idiopathic multiple pigment sarcoma (idiopathic multiple hemorrhagic sarcoma) of Kaposi. *Ibid.*, 17:135 (Apr.) 1905.

274. Webster, J.R. Sarcoma idiopathicum multiplex haemorrhagicum (Kaposi); variations from the usual clinical picture. *Arch. Dermat. & Syph.*, 30:383 (Sept.) 1934.

275. Wellman, G.L.: The clinical aspects of cardiac involvement (right auricular tumor) in idiopathic hemorrhagic sarcoma (Kaposi's disease). *Ann. Int. Med.* 14:314 (Aug.) 1940.

276. Wende, G.W. A case of multiple idiopathic pigmented sarcoma. *J. Cutan. Dis.*, 16:205 (May) 1898.

277. White, J. and Stewart, H.L. Intestinal adenocarcinoma and intraabdominal hemangioendothelioma in mice ingesting methylcholanthrene. *J. Nat. Cancer Inst.*, 3:331 (Dec.) 1942.

278. Wigley, J.E.M. Kaposi's idiopathic sarcoma. *Proc. Roy. Soc. M.* 39:227 (Dec. 20) 1945 and Idiopathic hemorrhagic sarcoma of Kaposi. *Ibid.*, 36:617 (May 20) 1943.

279. Wile, U.J. In discussion on Ormsby and Mitchell (186a)

280. Willis, R.A. The Pathology of Tumors. St. Louis, Mosby 1948, p. 80.

281. Willius, F.A. Clinic on refractory congestive heart failure of relatively short duration, comments, postmortem findings (primary fibrosarcoma of the right auricle). *Proc. Staff Meet. Mayo Clin.* 13:331 1938.

282. Winternitz, R. Multiples haemorrhagisches pigmentsarkom Kaposi. *Zentralbl. f. Haut. u. Geschl.* 24:161 1927

283. Winer, L.H.: Mycosis fungoides; benign and malignant cell dysplasia. *Arch. Dermat. & Syph.*, 56:460 (Oct.) 1947.

284. Wintrobe, M.M. and Huguley, C.M., Jr.: Nitrogen-mustard therapy for Hodgkin's disease, lymphosarcoma, the leukemias, and other disorders. Cancer 1:357, 1948.

285a. Wise, F. Idiopathic hemorrhagic multiple sarcoma of the skin (Kaposi) with special reference to early diagnosis. *M. Rec.*, 88:513, 1915.

b. Wise, F. Sarcoma of Kaposi. *Arch. Dermat. & Syph.*, 18:952 (Dec.) 1928.

c. Wise, F. Sarcoma of Kaposi with buccal lesion. *Ibid.*, 47:733 (May) 1943.

d. Wise, F. Multiple idiopathic hemorrhagic sarcoma of Kaposi with sarcoid-like changes in lymph nodes. *Ibid.*, 51:291 (Apr.) 1945.

e. Wise, F. and Eller, J.J. Bullous eruptions in hemorrhagic sarcoma of Kaposi and in lichen planus. *Ibid.* 7:625 (May) 1923.

286. Wood, F.C. Cited by MacKee and Cipollaro (155b).

287. Wolf, C. Idiopathic multiple hemorrhagic sarcoma of Kaposi. *Arch. Dermat. & Syph.*, 36:1252 (Dec.) 1937.

288. Wolf, J. In discussion on Rosen, I. Kaposi's sarcoma associated with lymphatic leukemia. *Arch. Dermat. & Syph.*, 48:566 (Nov.) 1943.

289a. Zakon, S.J. Kaposi's sarcoma. *Arch. Dermat. & Syph.* 42:19 (July) 1940.

b. Zakon, S.J. Idiopathic multiple hemorrhagic sarcoma of Kaposi. *Ibid.* 55:564 (Apr.) 1947.

c. Zakon, S.J. Kaposi's sarcoma with involvement of the gastrointestinal tract. *Ibid.* 57:475 (Mar.) 1948.

290. Zeisler, E.P. In discussion on Cornbleet (46).

291. Zimmerlich, L.: Multiples idiopathisches Hautsarkom mit Knochenmetastasen. *Arch. Dermat. u. Syph.* 107:329, 1911.

INDEX

K

L

M

N

O

P